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AN EVALUATION OF AUREOMYCIN THERAPY IN PRIMARY ATYPICAL PNEUMONIA*

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AUREOMYCIN has been reported as an effective agent in the therapy of primary atypical pneumonia.[1-6] Most observers have noted a consistent pattern of response, but only one study in which controlled observations were attempted has been presented.[5] Although the etiologic agent of this disease has not been established, investigators agree that it is probably a virus.[7] Eaton has also demonstrated that aureomycin protected cotton rats from infection with one of the viral agents isolated from cases of primary atypical pneumonia. In addition, cotton rats did not develop pneumonitis, when infected with inoculums prepared from infected chick embryos that had been treated with the antibiotic.[8]

The average duration of fever in primary atypical pneumonia is approximately ten days, with a range of seven to forty-nine days.[7] Since the mortality is low and complications are infrequent in this disease, objective evaluation is essentially limited to the duration of fever. The period in the natural course of the disease when therapy is initiated becomes an important factor. Patients treated late may become afebrile spontaneously, and no distinct difference from a comparable untreated group would be evident. The observations on hospitalized cases alone introduce an artificial selection because patients who have received nonspecific antibiotic therapy or whose fever terminated early spontaneously are not included in the study group. The duration of the febrile period in any group under observation in the hospital will thus be a function of the day of disease when the patients were hospitalized as well as the time when specific therapy was instituted. Also, comparison of non-hospitalized cases with hospitalized cases would not be valid.

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An attempt to evaluate the efficacy of aureomycin when compared to therapy believed not to possess specific activity, such as the sulfonamides or penicillin, is difficult unless two populations are available that are comparable in all respects in factors that may alter the course of the disease — for example race, age distribution, severity, therapy and general medical care. Such conditions may prevail in certain populations, in institutions or the armed forces, but not among the civil population. In contrast, the patients requiring hospital care from among the general civil population are often more severely ill. During the period 1946 through 1947 a total of 22 patients with diagnoses of primary atypical pneumonia were admitted to the Sinai Hospital in Baltimore. All but 1 of these received penicillin or sulfonamide therapy at some period of the illness. From September, 1948, to September, 1949, in 33 consecutive cases of primary atypical pneumonia the patients received only aureomycin therapy during the period of observation in the hospital. The comparative results in these two series were analyzed to determine whether aureomycin exerted any beneficial effect on the course of the disease as seen on the medical service of a general hospital. All patients were hospitalized. They were admitted to both the wards and the private services. All, except 1, had confirmatory evidence of pneumonia on x-ray examination. The case without x-ray confirmation showed definite signs of pulmonary consolidation on physical examination.

The diagnosis of primary atypical pneumonia was established on the basis of history, physical examination and laboratory studies.[2] The onset of illness was usually gradual, with fever, nonproductive cough, headache, malaise, chilly sensations and occasional substernal pain. Physical examination initially revealed minimal pulmonary signs in contrast to the more extensive involvement demonstrated by x-ray study. The physical signs of pulmonary consolidation became more evident later in the course of the illness.

Laboratory investigations are summarized in Tables 1, 2 and 3. An absence of leukocytosis was

evident, the white-cell counts varying between 3000 and 14,650. Ten of the 55 patients had an initial leukocyte count in excess of 10,000. Nasopharyngeal, throat, sputum and blood culture was performed before therapy. All blood cultures were sterile. The pathogenic organisms commonly associated with pneumonia were generally absent from cultures obtained from the nasopharynx, throat and sputum. Two patients showed pneumococcus Types XIII and XVI, respectively, in the sputum, and a beta-hemolytic streptococcus was isolated from the nose and throat cultures in 3 cases. These patients were in Group I (1946–47) receiving penicillin and sulfonamide treatment. Four patients who were treated with aureomycin in 1948–49 had initial sputum, nose or throat cultures containing beta-hemolytic streptococci.

Serial examinations of the serums for development of cold hemagglutinins were performed, and 54.5 per cent of the patients had a titer of 1:32 or higher. Other serologic tests were performed for heterophil, psittacosis, Q fever and influenza-virus antibody, but all were negative and are not reported in detail.[2]

The two groups were comparable in sex, age, degree of pulmonary involvement, fever on admission and duration of disease before hospitalization. These data are summarized in Tables 4 and 5. All the patients observed were of the white race. Forty-six per cent of each group were male, and 54 per cent were female patients. The median age of the group treated in 1946–47 was thirty-one years. The youngest patient was eight, and the oldest sixty-five years of age. Six patients were under twenty years of age, 9 were between twenty and forty years, and 7 were older than forty years. The median age of the aureomycin-treated group was forty-one years, with a range of five to seventy-three years. Six patients were under twenty years of age, 10 were between twenty and forty years, and 17 were over forty years of age. The median temperature upon admission to the hospital was 103.8°F. for Group I and 103.6°F. for the aureomycin-treated group. The extent of pulmonary involvement on x-ray examination in both groups was comparable: 73 per cent of patients in Group I (not receiving aureomycin) had a single lobe involved, and 27 per cent showed pneumonic infiltration of more than one lobe; among the patients in Group II, who received aureomycin, 70 per cent had single-lobe and 30 per cent had evidence of multiple-lobe involvement. The development of cold hemagglutinins to a titer of 1:32 or greater was observed in 59 per cent and 52 per cent of the two groups respectively. The median day of hospitalization was the 5th day (average 6.6 ± 0.83) for the 1946–47 group and the 4th day (average 4.8 ± 0.66) for the group receiving aureomycin. Treatment with the antibiotic was initiated on the 5th day (average 6.6 ± 0.61 days). Fifteen

TABLE 1. *Laboratory Data in Patients with Atypical Pneumonia not Receiving Aureomycin (Group I, 1946–1947).*

PATIENT	AGE	SEX	DAY OF DISEASE ADMITTED	ADMISSION TEMPERATURE	CULTURES	WHITE-CELL COUNT
	yr.			°F.		
E. C.	33	F	5	104.0	Negative	10,200–6200
D. M.	14	F	5	104.0	Negative	6900–7000
H. F.	36	M	5	104.0	Beta-hemolytic streptococcus in nose and throat	7000–5300
R. D.	27	F	14	100.4	Negative	9200
M. W.	65	M	3	102.0	Negative	9100–12,300
T. W.	8	F	5	104.0	Negative	6100–7800
G. G.	31	F	3	103.6	Negative	11,900–6100
N. K.	40	M	5	103.0	Negative	11,800–5700
P. P.	58	M	2	104.8	Beta-hemolytic streptococcus in nose and throat	9700–4800
J. K.	35	M	5	103.8	Negative	13,200
E. W.	23	M	7	102.0	Negative	7350 5000 14,400
L. G.	16	M	5	103.6	Negative	4400–7600
H. W.	31	F	6	103.4	Negative	5000–12,900
N. F.	18	F	7	103.8	Pneumococcus, Type 13, in sputum	5500–7400
M. M.	15	F	7	104.0	Negative	7200–9750
C. W.	41	M	8	104.0	Negative	5000–9500
L. K.	27	F	8	102.4	Negative	7650–6500
A. W.	57	F	20	101.0	Negative	6300–5300
I. C.	42	F	5	101.0	Negative	9500–5200
A. B.	28	M	9	104.0	Negative	9300–7200
R. L.	40	F	3	105.0	Negative	7300–9200
I. W.	18	M	8	100.4	Beta-hemolytic streptococcus in nose and throat; pneumococcus, Type 16, in sputum.	14,000–5200

of the 22 patients (68.2 per cent) treated during 1946–47 received penicillin or sulfonamide therapy or both, before hospitalization, and 23 of the 33 patients (69.4 per cent) had received similar therapy preceding their hospitalization in 1948–49. The major criticism inherent in the comparison of the two groups of patients is the difference in time at which they were ill. There is no evidence that the severity or course of the disease varied between 1946–47 and 1948–49, but the possibility exists.

The dosage of aureomycin employed for therapy varied considerably, owing to the amount available, the size of the prepared capsules and the severity of the disease. In general, an initial priming dose of 250 mg. each hour for three or four doses was followed by 250 mg. every two hours for the ensuing day. A few patients were maintained on this dosage schedule for several days, but in the majority, therapy was continued with 250 mg. every 4 to 6 hours. The average duration of aureomycin therapy was 5 days, and the mean amount of antibiotic administered to a patient was 7.2 gm. As preparations of aureomycin that caused less nausea became available, larger doses of 0.5 gm. every 4 to 6 hours were used. Only the oral route for the administration of aureomycin was employed.

The results observed in the two groups indicate that aureomycin therapy exerted a distinct influence on the duration or fever in primary atypical pneumonia. The pertinent observations are summarized in Table 5 and Figure 1. The significant data for each patient are presented in Tables 1, 2 and 3. In addition, symptomatic improvement appeared to parallel the febrile course. Because of the lack of reliable objective criteria, the effect of aureomycin on the paroxysmal cough and rate of clearing on x-ray examination could not be evaluated. However, no increase in cough or progression of pulmonary involvement, which had been frequently noted when penicillin was employed, was noted after the institution of aureomycin therapy. It was our impression that aureomycin exerted a favorable effect.

The total duration of the disease in Group I varied from 7 to 26 days. The median duration was 11 days (first and third quartiles, 10 to 14 days). The median duration of disease is often preferable in this type of data because it is not distorted by a few unusual values. However, the arithmetic mean is more familiar and is generally employed. In this group, the average duration of disease was 13 days, and the standard error of the mean was 0.94 day. The patients had been hospitalized on the second to twentieth days of disease, with the median on the fifth day and the mean 6.6 ± 0.83 days. Therapy with penicillin or sulfadiazine, when employed after hospitalization in this group, was initiated soon after admission to the hospital. Many patients had been receiving

TABLE 1 (*Concluded*).

PATIENT	PULMONARY INVOLVEMENT	COLD-AGGLUTININ TITER	TREATMENT			RESULT
			BEFORE HOSPITALIZATION	DAY OF DISEASE INITIATED	IN HOSPITAL	DAY OF DISEASE PATIENT AFEBRILE
E. C.	Left lower lobe	Negative	Sulfonamide	5	Penicillin for 8 days	11
D. M.	Left upper and right lower lobes	1:128 to 1:256	Sulfonamide	5	None	16
H. F.	Right upper lobe	Negative	Penicillin and sulfonamide	5	None	10
R. D.	Left lower lobe	1:128	Penicillin	14	Penicillin for 4 days	15
M. W.	Right lower lobe	1:256	None	3	Penicillin for 11 days	11
T. W.	Right lower lobe	1:256	Sulfonamide	5	Penicillin for 7 days	12
G. G.	Left lower lobe	Negative	Penicillin and sulfonamide	3	Penicillin for 4 days	8
N. K.	Left lower lobe	Negative	None	5	Sulfonamide for 4 days	7
P. P.	Right lower lobe	Negative	None	2	Sulfonamide for 6 days; penicillin for 8 days.	12
J. K.	Right lower lobe	Negative	Sulfonamide	5	Sulfonamide for 5 days; penicillin for 4 days.	11
E. W.	Right upper and right lower lobes	0 to 1:512	None	7	Sulfonamide for 8 days; penicillin for 5 days.	7½
L. G.	Left lower lobe	1:512	Penicillin and sulfonamide	5	None	10
H. W.	Left lower lobe	0 to 1:512	Sulfonamide	6	Penicillin for 6 days	19
N. F.	Left lower lobe	0 to 1:256	Penicillin and sulfonamide	7	Penicillin for 5 days	14
M. M.	Right lower lobe	1:512 to 1:4096	Sulfonamide	7	Penicillin for 9 days	13
C. W.	Left lower lobe	Negative	Penicillin and sulfonamide	8	Penicillin for 7 days; sulfonamide for 4 days.	12
L. K.	Left upper and left lower lobes	1:256 to 1:512	None	8	Penicillin for 5 days	26
A. W.	Left lower and right lower lobes	Negative	Penicillin	20	None	24
I. C.	Left lower lobe	Negative	None	5	None	7
A. B.	Right lower and left lower lobes	1:128 to 1:1024	Penicillin and sulfonamide	9	Penicillin for 3 days	13
R. L.	Right middle and right lower lobes	1:512 to 1:1024	Penicillin	3	Penicillin for 10 days	16
I. W.	Right lower lobe	1:128	None	8	Penicillin for 7 days	11

these therapeutic agents prior to hospitalization, and these were continued after admission. The duration of the febrile period after hospitalization was 0.5 to 18 days, with a median of 5 days. The mean period was 6.4 days with a standard error of ± 0.85 day.

The patients in Group II, treated with aureomycin after hospitalization, were admitted on the 1st to the 21st day of disease. The median day of admission was the 4th day, and the mean day was 4.8, with a standard error of ± 0.66 day. If, however, the day when aureomycin therapy was initiated is considered, the median day for this group was the 5th day, and the average duration of disease was 6.1 ± 0.66 days. One patient, who received aureomycin for 2 days with remission of symptoms and later relapsed, prior to hospitalization, is considered in this group as having been ill for the entire period and treated only after hospitalization. None of these patients had shown defervescence before aureomycin therapy was begun.

The 33 patients treated with aureomycin were febrile for 0.5 to 12 days after hospitalization, the median being 2.5 and the mean duration of fever 3.1 ± 0.07 days. When the period of fever following the initiation of aureomycin therapy is considered, the range was 0.5 to 7 days, with the median 1.5 and the mean, 1.8 ± 0.23 days. The total duration of fever from onset of illness to defervescence in this group varied from 3 to 21 days, with a median of 7 and a mean total duration of 7.8 ± 0.89 days.

When the groups were subdivided into patients who developed positive cold hemagglutinins and those whose serums did not agglutinate human Group O red cells in the cold, they were found to be comparable so far as the duration of disease before hospitalization was concerned. Those with

TABLE 2. *Laboratory Data in Patients with Atypical Pneumonia Treated with Aureomycin (Group II, 1948-1949).*

PATIENT	AGE	SEX	DAY OF DISEASE ADMITTED	ADMISSION TEMPERATURE	CULTURES	WHITE-CELL COUNT
	yr.			*°F.*		
L. M.	48	F	21	100.0	Negative	11,000–8000
F. S.	33	F	14	100.0	Negative	9700–7500
H. S.	73	F	6	101.5	Negative	14,650–10,750
S. S.	42	F	5	103.0	Negative	8000–7000
H. L.	17	M	3	103.5	Negative	8900–11,000
M. K.	43	M	5	103.5	Negative	13,950
R. P.	15	M	1	105.0	Negative	4950–8000
B. G.	44	M	6	104.5	Negative	5400–6250
C. B.	23	M	2	103.6	Beta-hemolytic streptococcus in nose and throat	10,000–7000
K. R.	5	M	7	102.0	Negative	6100–9050
T. B.	34	F	3	101.8	Negative	8400–5600
L. M.	13	M	2	104.2	Negative	6100
G. S.	70	M	1	102.4	Beta-hemolytic streptococcus in sputum	9250
P. S.	20	F	2	103.8	Negative	9400–6850
G. K.	43	M	6	102.4	Beta-hemolytic streptococcus in nose and throat	7950–10,550
J. M.	61	M	1	102.6	Negative	13,100–15,150
E. K.	52	M	4	104.4	Negative	8500–6650
J. S.	42	M	4	104.0	Negative	3000–11,400
E. C.	59	F	6	104.4	Negative	6100
S. L.	31	M	4	103.0	Negative	5400–9300
B. B.	41	F	4	104.0	Negative	6500–8700
F. K.	31	F	5	104.5	Alpha-hemolytic streptococcus and *Staph. aureus* in nose and throat	6900–9900
M. C.	24	M	8	105.0	Beta-hemolytic streptococcus and *Staph. aureus* in nose and throat; *Staph. aureus* in sputum.	7000–9600
I. C.	43	F	4	103.0	Negative	6250–6000
Z. S.	11	F	10	102.0	*Staph. aureus* in nose and throat	12,350–10,250
I. R.	43	F	4	104.0	Negative	6000–8600
S. J.	38	F	4	103.0	Negative	5050–8200
N. M.	19	F	2	104.4	Negative	8000
F. T.	54	F	3	103.6	Negative	8250–6440
M. H.	32	F	3	105.2	Negative	6050–11,400
A. R.	53	F	2	100.2	*Staph. aureus* in nose and throat; *Staph. aureus* in sputum.	9000–6250
N. L.	57	M	5	104.0	*Staph. aureus* in sputum	7200–3500
J. B.	67	F	2	100.0	Negative	4650–9100

*Single x-ray film normal: definite physical signs developed.

positive cold hemagglutinins (titer greater than 1:32) appeared to have a longer duration of febrile period in the hospital as well as total febrile period. This difference, as noted in Table 5, was more marked among the patients observed in 1946–47, who had not received aureomycin.

In Figure 1 the proportion of patients in each group who became afebrile at various periods after onset of illness is represented graphically. Although his therapy had been initiated on the 21st day of his illness. Twenty-three per cent of the patients who had not received aureomycin were still febrile from the 15th to the 26th day of illness. They had been hospitalized on the 3rd, 5th, 6th, 8th and 20th days of illness.

Six patients observed in 1948–49 were not included among the aureomycin-treated group because they had received both aureomycin and

TABLE 2 (*Concluded*).

PATIENT	PULMONARY INVOLVEMENT	COLD-AGGLUTININ TITER	TREATMENT			RESULT
			BEFORE HOSPITALIZATION	DAY OF DISEASE INITIATED	TOTAL DOSE OF AUREOMYCIN	DAY OF DISEASE PATIENT AFEBRILE
					gm.	
L. M.	Right lower lobe	Negative	Penicillin and sulfonamide	21	4.5 (4 days)	21½
F. S.	Right* and left lower lobes	Negative	Sulfonamide	14	1.75 (2 days)	14½
H. S.	Right and left lower lobes	Negative	None	6	3 (3 days)	10
S. S.	Right lower lobe	1:256 to 1:1024	Aureomycin (4 gm.) with remission and relapse	9	15 (5 days)	10
H. L.	Left lower lobe	0 to 1:128	None	3	8.5 (6 days)	4½
M. K.	Right middle lobe	Negative	None	5	6 (4 days)	5½
R. P.	Left lower lobe	0 to 1:128	Penicillin and sulfonamide	2	7.5 (5½ days)	3
B. G.	Right and left lower lobes	0 to 1:64	Penicillin and sulfonamide	6	17.5 (8 days)	13
C. B.	Right middle lobe	1:4 to 1:128	Penicillin and sulfonamide	2	17.0 (9 days)	3½
K. R.	Left lower lobe	0 to 1:2048	Penicillin	7	3.7 (5 days)	9
T. B.	Right middle and left lower lobes	1:8 to 1:256	None	3	17.75 (6 days)	7
L. M.	Right lower lobe	1:16	Sulfonamide	2	11.5 (4 days)	4
G. S.	Right and left lower lobes	Negative	Penicillin	3	11.75 (4 days)	6
P. S.	Right lower lobe	1:128	Penicillin	6	10 (7 days)	7
G. K.	Right middle lobe	0 to 1:1024	None	6	6.25 (5 days)	9
J. M.	Right and left lower lobes	1:8	Penicillin	10	16.75 (7 days)	13
E. K.	Left lower lobe	0 to 1:32	Penicillin	5	7.5 (6 days)	7½
J. S.	Right lower lobe	Negative	Penicillin and sulfonamide	5	15.25 (7 days)	7½
E. C.	Left lower and upper lobes	Negative	Penicillin and sulfonamide	7	7.6 (3 days)	8½
S. L.	Right upper lobe	Negative	None	4	4.4 (2 days)	5
B. B.	Left lower lobe	0 to 1:512	Penicillin and sulfonamide	8	8 (5 days)	9
F. K.	Right upper lobe	Negative	Penicillin	6	4.9 (3 days)	7
M. C.	Left upper and lower and right middle lobes	0 to 1:512	Penicillin and sulfonamide	9	11 (6 days)	12
I. C.	Right and left lower lobes	Negative	None	5	7.75 (4 days)	7½
Z. S.	Left lower lobe	0 to 1:512	Penicillin	10	5.25 (4 days)	10½
I. R.	Left lower lobe	0 to 1:1024	Penicillin	7	7.25 (4 days)	8½
S. J.	Left lower lobe	Negative	Penicillin	5	5.6 (4 days)	6
N. M.	Left lower lobe	Negative	Penicillin	2	7 (4 days)	3
F. T.	Right middle lobe	Negative	Penicillin	4	5 (3 days)	5½
M. H.	Right lower lobe	Negative	None	3	7 (4.5 days)	3½
A. R.	Right upper lobe	1:2048	Penicillin	7	8.75 (8 days)	7½
N. L.	Right and left lower lobes	0 to 1:512	Penicillin and sulfonamide	6	5.9 (2 days)	7
J. B.	Right and left lower lobes	1:32–1:64	None	3	11 (6 days)	5

there was little difference in the duration of disease before hospitalization between the two groups, 66.3 per cent of the aureomycin-treated patients were afebrile by the 8th day of illness, whereas only 18.2 per cent of those who had not received aureomycin were afebrile. On the 11th day of disease, 50 per cent of the 1946–47 group, and 84 per cent of the aureomycin-treated group were afebrile. After the 14th day of disease, only 1 patient treated with aureomycin was still febrile, and penicillin therapy throughout their course of hospitalization. Three were males, and 3 were females. They had been ill for 2 to 10 days, with a median period of 4 or 5 days before being hospitalized. The median temperature on admission was 103.4°F., and 3 of the 6 patients developed a cold hemagglutinin titer greater than 1:32. The febrile period in the hospital varied from 0.5 to 3 days, and the total duration of febrile illness ranged from 4.0 to 11.5 days with a mean duration of 6.5 days.

The results in this group were essentially the same as those observed when only aureomycin was employed.

Aside from unpleasant side effects of nausea, anorexia, vomiting, diarrhea and perianal irritation, frequently reported after the oral administration of aureomycin, no toxic manifestations were observed. Thirty-three per cent of the patients experienced nausea to some degree, 12.8 per cent vomited, and 12.8 per cent had frequent bowel movements. Aluminum hydroxide preparations such as Amphojel (½ ounce) were employed when the nausea became severe. The routine use of these antacid preparations is not advisable in the light of the observations that absorption of aureomycin may be diminished.[9, 10] The nausea may be minimized through the use of small doses of the antibiotic given at more frequent intervals. The incidence of nausea has been reduced materially when the recrystallized aureomycin, at present available, has been employed.

The observations presented in this study confirm previous reports that aureomycin shortens the duration of the febrile period in primary atypical pneumonia. Although the group treated in 1946–47 is quite comparable to the group treated with aureomycin in 1948–49 in sex, age, temperature on admission, degree of pulmonary involvement, day of disease when hospitalized and proportion developing cold hemagglutinins to a significant titer, the chronologic separation is a distinct disadvantage. Our efforts to conduct this type of study with treatment of alternate patients have been unsuccessful. Patients are not admitted to the hospital from the community at a uniform rate or in sufficient number; they may be ill for varying periods, and the influence of preceding therapy is difficult to assess. Even in the study conducted among Army personnel, 4 patients in the penicillin-treated group were given aureomycin because of the severity of illness and the persistence of fever. The unconscious selection of subjects for therapy

TABLE 3. *Laboratory Data in Patients Given Combined Therapy, Aureomycin and Penicillin, Group III, 1948-49.*

PATIENT	AGE	SEX	DAY OF DISEASE ADMITTED	ADMISSION TEMPERATURE	CULTURES	WHITE-CELL COUNT	PULMONARY INVOLVEMENT	COLD AGGLUTININ TITER	TREATMENT			RESULT
									PRE-HOSPITAL	DAY DISEASE INITIATED	IN HOSPITAL	DAY OF DISEASE PATIENT AFEBRILE
	yr.			°*F.*								
L. E.	21	M	10	100.8	Negative	8480	Right and left lower lobes	1:2048	Penicillin	10	Aureomycin, 14.25 gm. (8 days); penicillin for 8 days.	11½
H. W.	67	M	5	105.0	*Staph. aureus* in nose and throat	8850–5450	Right lower lobe	Negative	None	5	Aureomycin, 5.5 gm. (3 days); penicillin for 3 days.	6
M. M.	25	F	2	103.4	Negative	10,550–5450	Right and left lower lobes	1:256	None	2	Aureomycin, 11.5 gm. (3 days); penicillin for 7 days.	5
S. G.	65	F	6	101.0	Negative	7400–5250	Right middle and left lower lobes	1:32	None	6	Aureomycin, 3.75 gm. (2 days); penicillin for 7 days.	6½
H. P.	80	F	2	105.0	*Staph. aureus* in nose and throat	10,450–3600	Right lower lobe	Negative	None	2	Aureomycin, 14.25 gm. (9 days); penicillin for 7 days.	5
M. W.	40	M	2	103.4	*Staph. aureus* in nose and throat	5500	Right lower lobe*	Negative	None	2	Aureomycin, 2.5 gm. (2 days); penicillin for 5 days.	4

*Single x-ray film normal; definite physical signs developed.

TABLE 4. *Comparison of Aureomycin-Treated and Nonaureomycin-Treated Cases of Atypical Pneumonia.*

GROUP	TOTAL NO. OF PATIENTS	MALE PATIENTS	FEMALE PATIENTS	MEDIAN AGE	MEDIAN TEMPERATURE ON ADMISSION	LOBES INVOLVED		PATIENTS WITH COLD-AGGLUTININ TITER OF 1:32
						SINGLE	MULTIPLE	
		%	%	*yr.*	°*F.*	%	%	%
I (1946–47)	22	46	54	31	103.8	73	27	59
II (1948–49)*	33	46	54	41	103.6	70	30	52

*Aureomycin therapy.

cannot be evaluated. The comparison with a preceding consecutive experience has the advantage that bias in the selection of cases is avoided. The course of primary atypical pneumonia has not varied appreciably in consecutive years. This type of analysis utilizing the experience of former years has frequently been employed in the study of pneumonia.

The aureomycin-treated group and the patients not receiving aureomycin therapy, did not differ significantly in the duration of disease before hospitalization. The day of disease on which aureomycin therapy was initiated almost coincided with the day of hospitalization of the nonaureomycin-treated group. The duration of fever after hospitalization was 3.1 ± 0.07 days for the patients receiving aureomycin, but only 1.8 ± 0.23 days if only the period after aureomycin therapy is considered. In contrast, the patients in Group I were febrile for an average period of 6.4 ± 0.85 days after hospitalization. When the total duration of disease is similarly compared, the patients not receiving aureomycin were febrile for an average period of 13.0 ± 0.94 days, whereas the aureomycin-treated patients were febrile for 7.8 ± 0.89 days. The differences observed in this study in respect to total duration of disease or febrile period after hospitalization are significant and would occur less than once in 3000 trials because of chance variation.

Summary

Twenty-two consecutive hospitalized patients ill with primary atypical pneumonia were observed in 1946–47, and 33 consecutive patients who received only aureomycin therapy after hospitalization during 1948–49 were studied. Six patients treated with both penicillin and aureomycin concomitantly were not included in either group but were considered separately. The groups were comparable in sex, age, duration of disease before hospitalization, temperature on admission, degree of pulmonary involvement and proportion developing cold hemagglutinins. The average duration of fever during the hospital period was 6.4 ± 0.85 days for the group treated in 1946–47 and 3.1 ± 0.07 days for the aureomycin-treated patients. The average duration of fever in the latter group was 1.8 ± 0.23 days after the beginning of aureomycin therapy.

The total duration of the febrile period was also materially shortened in the aureomycin-treated group, with an average period of 7.8 ± 0.89 days from onset of illness to defervescence. In contrast, the patients not receiving aureomycin were febrile for an average period of 13.0 ± 0.94 days.

No significant toxic reactions to the aureomycin therapy were noted, although 33 per cent of the

Table 5. *Influence of Aureomycin Therapy.*

Cold-Agglutinin Titer	No. of Patients	Duration of Disease before Hospitalization or Aureomycin Therapy			Duration of Fever after Hospitalization or Aureomycin Therapy			Total Duration of Fever after Onset of Illness		
		range	median	mean ±1†	range	median	mean ±1†	range	median	mean ±1†
		days	*days*	*days*	*days*	*days*	*days*	*days*	*days*	*days*
Group I (1946-47):										
Negative	9	2–20	5	6.4	2–10	5	4.9	7–24	11.0	11.3
Positive	13	3–14	7	6.6	0.5–18	7	7.5	7.5–26	13.0	14.2
Totals	22	2–20	5	6.6 ± 0.83†	0.5–18	5	6.4 ± 0.85†	7–26	11.0	13.0 ± 0.94†
Group II (1947-48):										
Negative	16	1–21	5	5.3	0.5–12	2	2.6	3.5–21	7.0	8.0
Positive	17	1–10	4	4.4	0.5–7	3.5	3.5	3–13	7.5	7.8
Totals	33	1–21	4	4.8 ± .66†	0.5–12	2.5	3.1 ± 0.07†	3–21	7.0	7.8 ± 0.89†
Group II (1947-48):*										
Negative	16	2–21	5	6.4	0.5–4	1.5	1.6	3.5–21	7.0	8.0
Positive	17	2–10	6	5.8	0.5–7	1.5	2.0	3–13	7.5	7.8
Totals	33	2–21	5	6.1 ± 0.66†	0.5–7	1.5	1.8 ± 0.23†	3–21	7.0	7.8 ± 0.89†

*Figures on duration of disease and fever pertain to institution of aureomycin therapy.
†Standard error.

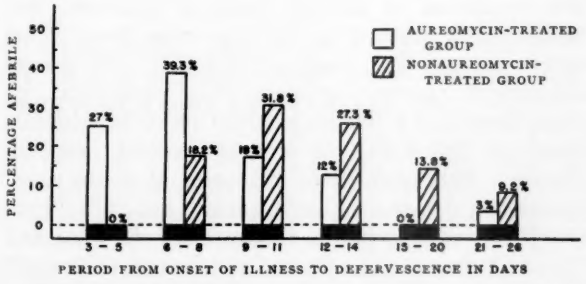

Figure 1. *Effect of Aureomycin Therapy in Primary Atypical Pneumonia, Showing Period of Illness at Which Various Proportions of Each Group Became Afebrile.*

patients complained of nausea, 12.8 per cent vomited and 12.8 per cent experienced mild diarrhea.

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EXPERIENCES WITH DICUMAROL IN ACUTE MYOCARDIAL INFARCTION*

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BOSTON

NUMEROUS reports[1-6] during the past few years have emphasized the value of Dicumarol therapy in reducing the mortality rate and the incidence of thromboembolic complications following acute myocardial infarction. These series have in general represented carefully followed cases under the direct supervision of well organized research teams, and results as reported have been favorable. Consequently, the statement has been made that Dicumarol therapy is indicated in every case of myocardial infarction in which proper laboratory facilities are available.

However, modes of therapy that work well under research conditions may not be so successful under the conditions of average hospital practice. Accordingly, it seemed advisable — even three years ago — to test the practicability and efficacy of Dicumarol therapy in myocardial infarction by employing it as a routine medication to be administered on the wards of a busy general hospital. Between 1946 and 1948, 250 cases of acute myocardial infarction — 122 "treated" and 128 "control" — were followed on the wards of the First and Third (Tufts) and the Second and Fourth (Harvard) Medical Services at the Boston City Hospital with this point in mind. A discussion of the difficulties, limitations and dangers encountered when Dicumarol is used without special supervision is the object of this report, since the practical difficulties in the use of this medication appear to deserve reemphasis.

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Methods

For the first year of this study alternate patients with acute myocardial infarction arriving on each ward were treated with Dicumarol. During the second year all such patients arriving on alternate days were so treated. The change was effected merely to facilitate proper count.

All patients who died in the first three days of their illness or within the first two days after admission to the hospital were excluded from both control and treated groups. Such patients would have derived no benefit from an anticoagulant that produces an appreciable effect only after two or three days. Also excluded from both groups were patients whose acute infarction occurred more than five days before admission, for it was believed that anticoagulant therapy initiated after this period would be of questionable value in preventing mural thrombi. Patients were otherwise entirely unselected except for the exclusion of all without supporting electrocardiographic evidence of the diagnosis.

The usual contraindications to Dicumarol therapy were posted on each ward — namely, hepatic or renal insufficiency, purpura of any type, blood dyscrasia with hemorrhagic diathesis, subacute bacterial endocarditis and recent operation on the brain or spinal cord. In addition, particular caution was to be observed in patients with ulcerative lesions or open wounds and with dietary or nutritional deficiency, and in the presence of drainage tubes.

It might be noted here that Dicumarol was administered without mishap to several patients with peptic ulcer and to others with initially low prothrombin levels and questionable hepatic status.

The general plan of administration consisted of an initial dose of 300 mg. as soon as the diagnosis was made, either clinically or by electrocardiogram. Provided the prothrombin level, submitted before the initial dose of Dicumarol, was not too low, 200 mg. was given on the second day. Thereafter, the dosage was roughly guided by the prothrombin level. If prothrombin activity was over 50 per cent of normal, the dose was 200 mg., if between 50 per cent and 35 per cent, 100 mg., if between 35 per cent and 20 per cent 50 mg., and if below 20 per cent none. Over week ends, when prothrombin determinations were unavailable, the dosage was guided by the patient's previous response to therapy and by the trend of the prothrombin levels at the time.

The laboratory employed the Quick[7] method of determining prothrombin time on undiluted plasma; ground, desiccated rabbit brain was used as the source of thromboplastin. A normal control blood specimen was tested each day. Clotting times on patients' plasma were translated into percentage of normal prothrombin activity by means of dilution curves previously established by dilution of normal plasma with prothrombin-free plasma.[8]

Results

Of the 250 cases included in the present study, 122 were treated with Dicumarol, and 128 were treated without anticoagulants as "controls." The two groups showed no significant difference regarding sex, age or average length of hospital stay, either in fatal cases or in survivors.

The average duration of administration was twenty-seven days in surviving patients and eleven days in those dying under treatment. The average daily dose ranged from 34 to 150 mg., reflecting the well known variability in individual response to Dicumarol.

Twenty-six of the 128 control cases (20.3 per cent) experienced 32 thromboembolic episodes (Table 1). Nineteen of the 122 treated cases (15.6 per cent) had 26 such episodes complicating their course. What appears striking is the greater incidence of peripheral arterial emboli and of detectable phlebothrombosis in the control group.

Dicumarol therapy did not improve the mortality (Table 2). The 18.9 per cent mortality in the treated group (as compared with 12.5 per cent in the control group) is partly a reflection of the fact that the anticoagulant was administered out of turn to some of the more severely ill patients. This may be seen, for example, in the greater number of patients in the treated group who died of congestive cardiac failure. In addition, 2 of the 23 deaths in the treated groups must be ascribed to the anticoagulant itself. On the other hand, 2 of the 16 deaths in the control group followed long hospitalizations for unrelated causes — 1 from carcinoma of the rectum and 1 from multiple myeloma.

It is of some significance, however, that 6 of the 16 deaths (37.5 per cent) in the control group were directly attributable to thromboembolic phenomena. Four of the 23 deaths in the treated group (17.4 per cent) could be so attributed.

Another favorable point for Dicumarol therapy is the 19 autopsied cases (Table 3). Of the 8 control cases studied after death, 6 (75 per cent) gave evidence of thromboembolic manifestations. Of the 11 treated cases, only 4 (36.4 per cent) had such evidence; all 4 showed mural thrombi in the ventricles.

Complications of anticoagulant therapy were encountered in 10, or 8.2 per cent, of the 122 patients to whom Dicumarol was administered

Table 1. *Thromboembolic Episodes.*

Episode	Control Cases	Treated Cases
Pulmonary embolus	11	14
Peripheral arterial embolus (other than cerebral)	4	1
Phlebothrombosis	9	2
Cerebrovascular accident (other than hemorrhagic)	2	6*
Further myocardial infarction	6	3
Totals	32	26

*1 was a known embolus.

Table 2. *Causes of Death.*

Cause	Control Cases	Treated Cases
Thromboembolus:		
Pulmonary embolus	1	0
Peripheral arterial embolus	2	1
Further myocardial infarction	3	1
Cerebrovascular accident	0	2
Sudden, unexplained	4	8
Shock	2	3
Congestive cardiac failure	1	4
Hypoprothrombinemia	0	2
Arrhythmia	1	0
Carcinoma of rectum	1	0
Multiple myeloma	1	0
Myocardial rupture	0	2
Totals	16	23

Table 3. *Data from Post-Mortem Examinations.*

Datum	Control Cases	Treated Cases
Number	8	11
Thromboembolic manifestations	6 (75%)	4 (36.4%)
Mural thrombus	3	4
Pulmonary embolus	2	1*
Venous thrombus	0	1*
Cerebral infarct	1	1*
Renal and splenic infarct	0	1*

*All in same case — 1 cerebral embolus on Dicumarol, and all the rest after anticoagulant was stopped.

(Table 4). Two of these 10 patients died, probably as a result of the treatment.

Discussion

The most striking point discovered in analysis of the results was the general lack of success in maintaining even and consistent prolongation of prothrombin times to therapeutic levels. Although some of the difficulty in maintaining low prothrombin levels has been mentioned in previous reports, the practical difficulties encountered have not been sufficiently emphasized.

Optimum levels of prolongation of prothrombin time have been worked out only empirically. The consensus at present is that levels between 15 and 30 per cent of normal prothrombin activity are optimum for preventing thromboembolism on the one hand and for obviating the dangers of hemorrhagic complications on the other. When the present study was initiated, levels of 30 to 50 per cent were considered adequate. During the second year, however, the lower levels were sought. Whatever the goal, intended levels were attained in most of the patients for varying periods, but they were only rarely maintained consistently. Less than 10 per cent of the cases could be said to have been under consistently good control of prothrombin levels. There are many reasons for the difficulty to be encountered in attempting to maintain prothrombin activity at adequate therapeutic levels. The most obvious is to be found in the widely variable individual differences in response and tolerance to the drug. This has been repeatedly observed by others and makes imperative completely individualized therapy.

Table 4. *Complications of Dicumarol Therapy.*

Complications	No. of Cases
Ecchymosis	1
Microscopical evidence of hematuria	4
Epistaxis	1*
Hematoma	1
Subconjunctival hemorrhage	1
Hemorrhage into ovarian cyst	1
Cerebral hemorrhage	1*
Totals	10 (8.2%)

*Patient died.

As in most general hospitals where the house and visiting staffs rotate, any patient may be under the care of several different physicians during the course of his hospital stay. This likelihood is increased on the evenings and week ends, during which any given house officer or resident may be off duty. Furthermore, house and visiting staffs have been generally inexperienced in the use of Dicumarol. This combination of inexperience and divided responsibility can lead to widely divergent degrees of caution in interpreting laboratory reports and translating them into Dicumarol dosage. In addition, divided responsibility and simple forgetfulness can result in failure to submit a patient's blood for determination of prothrombin activity on a given day. As a consequence, either no Dicumarol or an inadequate amount is given by the more cautious, or perhaps even an excessive dose may be given by the less cautious.

An all too common failing is to allow prothrombin activity to rise above the low therapeutic levels before continuing the administration of adequate dosage of Dicumarol. The latent period of effectiveness of the anticoagulant then allows the level to rise even higher for the next day or two. This results in a "picket-fence" graph of daily prothrombin activity. Experience with this medication teaches one to adjust daily dosage to "trends" in prothrombin levels as much as to actual levels reported on any one day. Posting detailed instructions on each ward and conducting discussions with the house staff are not enough to replace the close supervision of all Dicumarol therapy by one or two well informed persons.

Another source of error is illegible handwriting on nurses' order sheets or careless scrutiny thereof. For instance, Demerol, in doses of 50 to 100 mg., is also frequently ordered for patients with acute myocardial infarction. We encountered cases of mistaken identity, fortunately without serious consequences. However, the moral is obvious.

Other difficulties stem from the laboratory despite earnest and painstaking co-operation on the part of its personnel. The fact that prothrombin determinations may be unavailable over week ends and holidays speaks for itself. The laboratory at this hospital is, in all probability, of the same caliber as those of most general hospitals. Such a laboratory may be called upon to perform 30 to 50 prothrombin determinations daily in addition to other routine and specialized procedures. Such mass production certainly cannot enhance accuracy with an already notoriously temperamental test.

Detailed analysis of the records shows clearly the consequences of poor and inconsistent regulation of prothrombin levels. Among the treated patients who developed thromboembolic complications, only 2 were maintained consistently at levels below 30 per cent of normal. Several clear-cut cases may be found among the other 17 cases when a thrombosis or embolism occurred during or just after lapses of two or three days during which the levels had been allowed to rise to ineffectual heights. Two others occurred after cessation of Dicumarol therapy, and in 1 of these, therapy was stopped because of difficulty encountered with the required venipuncture.

The effect of adequate and inadequate maintenance of prothrombin levels is to be noted in the results of post-mortem examinations (Table 3).

Twenty-three treated patients died, and 11 of these were autopsied. In 7 no thrombi or emboli were found, and analysis shows that levels of prothrombin activity had been well controlled in these cases. Of the 4 patients in whom thromboembolic manifestations were found after death, 3 had been inadequately treated with Dicumarol. One of these chanced to be resistant to the medication in a dosage of 300 mg. initially followed by six daily doses of 200 mg., and obviously should have received more. The fourth, who showed a mural thrombus, was found to have had prothrombin levels below 30 per cent only on the fourth day of treatment with Dicumarol. Inasmuch as mural thrombus may form in the first twenty-four hours after the initial insult to the myocardium,[9] the mural thrombus in this case undoubtedly developed before the anticoagulant could possibly have prevented it. Such observations may well be a recommendation for heparin coincident with the initiation of Dicumarol therapy, to prevent, if possible, not only early mural-thrombus formation but also retrograde extension of the original clot in the coronary artery as brought out by Glueck and her associates.[10]

Finally, it is well to keep in mind the very real dangers in the use of Dicumarol when prothrombin levels cannot be very carefully supervised with complete confidence in all aspects of the program of treatment. We encountered the usually observed minor hemorrhagic complications (Table 4) besides one that was more unusual — namely, a rapid increase in size of a pelvic mass (in all probability hemorrhage into an ovarian cyst) accompanied by bleeding from the vaginal mucous membrane. In addition, injudicious, poorly regulated Dicumarol therapy contributed to 2 deaths. These deserve further mention.

One of these patients was "sensitive" to Dicumarol and was given 100 mg. by mistake on a day when the prothrombin level was reported as 20 per cent. Two days later, when the patient was found comatose, lumbar puncture revealed xanthochromic spinal fluid containing red blood cells. Death followed in two days, with a terminal rise in temperature to 107°F. — presumably from continued cerebral hemorrhage. No further prothrombin levels were recorded. Autopsy was not permitted.

The other fatal episode was ushered in by severe epistaxis when the prothrombin time was reported as 2 minutes and 45 seconds (control 17 seconds). This level followed the administration of one 50-mg. dose and one 100-mg. dose of Dicumarol on the two preceding days, on which no prothrombin levels were determined and prior to which the prothrombin level was 25 per cent of normal. Nasal packs, 120 mg. of synthetic vitamin K and 500 cc. of whole blood stopped the epistaxis in a few hours, but the patient gradually failed, dying in two days. The significant findings at autopsy were subendocardial hemorrhage and hemorrhage in the renal pelves, although neither site appeared to elucidate adequately the cause of death.

So much for the practical aspects of routinized Dicumarol therapy and its regulation by prothrombin determinations. Another word of caution is well brought out regarding possible inaccuracies in such a study. One major source of confusion is the subjective factor, which frequently plays a prominent part in the diagnosis of phlebothrombosis or pulmonary embolism. This is true no matter how well criteria for diagnosis may be set forth. Portable x-ray apparatus must be utilized in patients with acute myocardial infarction; the resulting chest plates are often too equivocal to be of use for the diagnosis of pulmonary infarction.

The question might also be raised regarding overenthusiasm, including both vigor and frequency, in palpating the calf muscles of patients in the control group of any such series. A greater incidence of phlebothrombosis may be expected in this group, and natural suggestibility on the part of the patients could lead to even greater confusion, as can easily be imagined. In addition, some calves may be actually made tender by the vigor of repeated palpations, and this is, after all, too often the only physical sign of phlebothrombosis. Despite the greatest care in reviewing the cases, the greater incidence of phlebothrombosis in the control group may be partly a reflection of the factors mentioned above. That the search for phlebothrombosis was not so avid in the treated patients is certainly to be suspected from the low incidence of phlebothrombosis in association with an even greater incidence of pulmonary embolism than was noted in the "control" patients.

It should be emphasized that these results in no way indicate that Dicumarol may not be of value in the treatment of patients with acute myocardial infarction. However, treatment with this anticoagulant must not be simply ordered and then forgotten. Constant, careful supervision of dosage and prothrombin levels is a prime requisite for successful results. For one period of several weeks in the early days of the study, one of us (E. B.) personally supervised all Dicumarol therapy on four of the wards involved in this study. During that time prothrombin levels were well controlled without much trouble. However, this procedure was discontinued, inasmuch as it was believed that a fair test of the practicability of any routine therapy must not involve its direct supervision by one person with a special interest in its application.

Summary

Under conditions of routine therapy, Dicumarol failed to improve significantly the prognosis of patients with acute myocardial infarction.

The apparent inefficacy of the anticoagulant was due for the most part to generally inadequate control of prothrombin levels.

The inconsistent maintenance of therapeutic levels of hypoprothrombinemia was due to many factors, which are discussed in detail.

The dangers in the inadequate supervision of Dicumarol therapy were emphasized by 2 deaths attributable to hypoprothrombinemia.

Post-mortem examination of 11 treated and 8 control cases showed the favorable effect of well controlled Dicumarol therapy in reducing the incidence of thromboembolic manifestations.

We are indebted to Drs. James M. Faulkner and Laurence B. Ellis for inspiration and guidance and to Dr. Stephen J. Maddock and Miss Dorothy Jensen, of the Surgical Research Laboratory, Boston City Hospital, in which the prothrombin determinations were performed, for their wholehearted co-operation.

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SPLENOMEGALY WITH HYPERSPLENISM DUE TO SARCOIDOSIS*

Report of a Case

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THE syndrome of hypersplenism has become well established as a clinical entity in the past few years by Dameshek,[1] Doan,[2, 3] Kracke[4] and others. A number of diseases of the spleen both primary and secondary, have been found to produce this syndrome of splenomegaly associated with cytopenias, either total or selective.[1-7] Although sarcoidosis has been known for many years to be a cause of splenic enlargement,[8-11] it is rare to find it associated with depression of the cellular elements of the blood.[5, 7, 12-14] In a search through the literature, only 6 cases of this syndrome due to sarcoidosis could be found.[5, 12-15] Recently, the following case of sarcoidosis of the spleen with hypersplenism was treated by splenectomy, with excellent results.

TABLE 1. *Hematologic Data before and after Splenectomy.*

DATE	RED-CELL COUNT	HEMOGLOBIN	WHITE-CELL COUNT	HEMATOCRIT	PLATELETS	SEDIMENTATION RATE	REMARKS
	$\times 10^6$	gm./100 cc.	$\times 10^3$	%		mm./hr.	
8/11/49	3.7	11.0	2.1	—	—	8	First admission
8/12/49	4.0	12.0	2.5	—	344,000	—	—
9/15/49	4.2	11.0	2.9	32	—	—	—
10/18/49	4.5	10.5	5.1*	—	186,000	—	Second admission
11/17/49	4.1	9.0	1.85	26	—	15	
11/18/49	—	9.5	2.2	—	380,000	—	Patient received 2000 cc. of blood before splenectomy, performed on this day
11/19/49	5.2	13.5	15.4	—	405,000	—	—
11/25/49	4.2	12.0	15.15	37	1,317,000	—	—
12/13/49	4.6	12.0	7.65	—	1,244,000	—	—
2/14/50	4.4	12.5	13.8	41	355,000	36	Third admission
2/16/50	—	—	11.8	—	—	—	—

*Count believed to be inaccurate.

CASE REPORT

A 62-year-old man was admitted to the hospital on August 10, 1949. In March he had noticed the gradual onset of a sharp stabbing pain in the left flank and consulted a physician, who told him that he had "spleen trouble." The pain gradually subsided for a period, but 2 months later a constant, dull heavy ache appeared in the same area. Weakness and mild anorexia developed, and in the next 3 months he lost 12 pounds in weight. One week prior to admission he became aware of a large, firm mass in the left upper quadrant of the abdomen.

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Physical examination showed a well developed and fairly well nourished man who complained of an ache in the left upper quadrant. Examination of the chest and heart revealed them to be normal. The liver was enlarged 4 cm. below the costal margin and was firm, smooth, and nontender. The spleen extended down to the pelvic brim and to the right 2 cm. beyond the midline. It was firm, fairly smooth, and with a palpable notch, and had a sharp border.

The temperature was 98.6°F., the pulse 94, and the respirations 18; the blood pressure was 128/68.

The laboratory data are shown in Table 1. A leukopenia and mild hypochromic anemia were present. Blood smears and platelet counts were normal. Repeated study of the urine and other kidney-function tests were negative. A battery of liver-function studies were within normal limits. The prothrombin, bleeding and clotting times were normal, and tourniquet tests and clot retractability tests were negative. The sedimentation rate was 8 mm. per hr. (Wintrobe method). A Wassermann test was negative, as well as numerous smears for malaria. Bone-marrow biopsy revealed a normoplastic marrow. X-ray examination of the chest was negative. X-ray films of the abdomen showed a tremendously

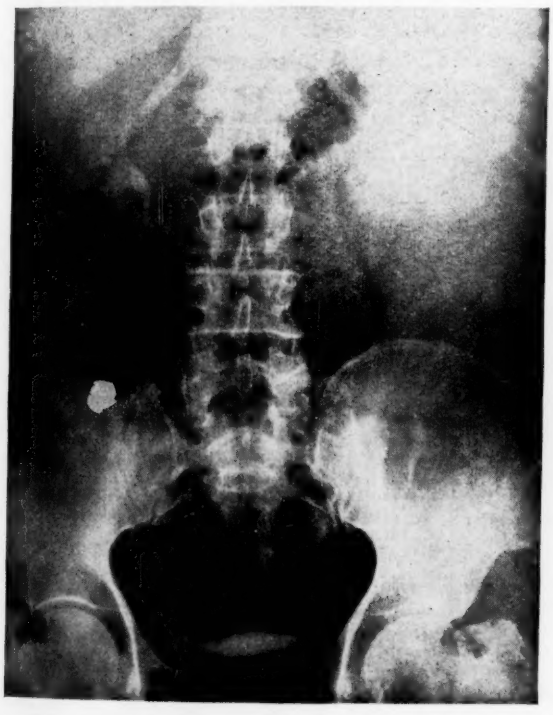

FIGURE 1. *X-Ray Film of the Abdomen, Revealing the Shadow of the Enlarged Spleen.*

enlarged spleen and an enlarged liver (Fig. 1). Intravenous pyelograms were normal.

During the hospital stay, the temperature remained normal, except for two occasions when it rose to 99.4°F. No specific therapy was given, and the pain gradually disappeared. The patient ate well and gained 2 pounds in weight. He was discharged after 44 days, to be followed as an outpatient.

Approximately 3 weeks later the pain returned with increased intensity so that he was unable to work. Along with this, some nausea, weakness and a few questionable night sweats developed. However, he lost no weight. He was readmitted to the hospital on October 17 for further studies. The physical findings were as before. All laboratory studies were repeated, and results were similar to those of the previous admission, except for an increase in the anemia. The leukopenia was still present (Table 1). A punch liver biopsy was performed, and the tissue was found to be normal histologically. For the most part the temperature was normal, but on occasions a low-grade fever, the cause of which could not be determined, developed. Because of persistent distressing symptoms, increasing anemia and leukopenia, splenectomy was believed to be indicated.

On November 18 splenectomy was performed without difficulty through a thoracoabdominal approach. The spleen extended from the dome of the diaphragm to the brim of the pelvis, and the capsule was smooth, with no adhesions. The

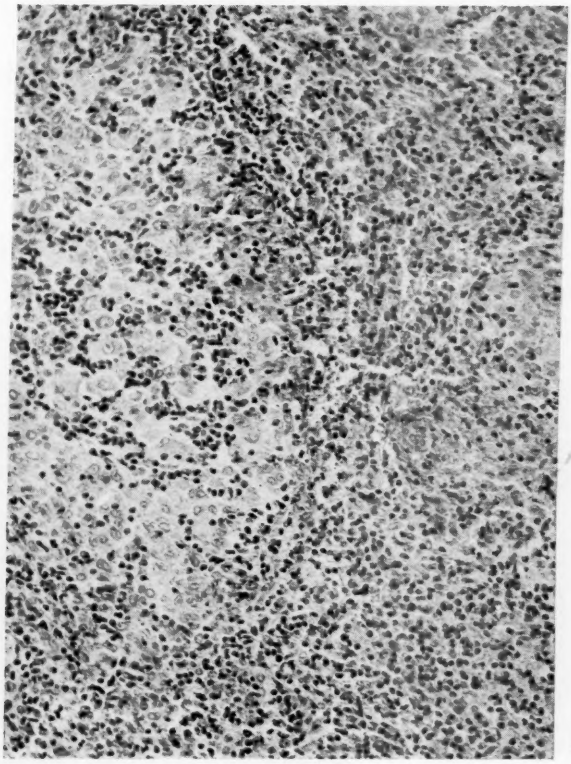

FIGURE 2. *Photomicrograph of the Spleen, Showing the Sarcoid Lesions (x200).*

liver was enlarged and smooth. Blood studies immediately after operation revealed a leukocytosis and an increase in platelets. No anemia was present, but this was attributed to transfusions given at the time of the operation. Subsequent studies are shown in Table 1.

On gross pathological examination, the spleen weighed 220 gm. The external surface was thickened, gray, opaque and of firm texture, with a purplish-gray color when cut.

Histologic examination revealed abundant malpighian corpuscles, variable in size and not uniform in structure. The majority of the corpuscles contained large, pale, foamy epithelial cells occupying the central portion and scattered diffusely through the follicles but some were arranged in concentric rings alternating with a ring of lymphocytes. In a few areas of the pulp, there were collections of large, pale cells, without any line of demarcation as a follicle except the presence of an outer ring of lymphocytes. Special stains for acid-fast organisms were negative. Although there were no fully organized sarcoid tubercles, it was believed that this was a case of sarcoidosis of the spleen (Fig. 2 and 3). Consequently, the slides were submitted to a number of recognized pathologists throughout the country and

to the Armed Forces Institute of Pathology, and the majority concurred with the pathological diagnosis of sarcoidosis of the spleen.

Convalescence was uneventful. Repeat x-ray examination of the chest revealed only a small left pleural effusion attributed to the operation. On December 17 the patient was discharged in an asymptomatic state.

He was readmitted to the hospital on February 12, 1950, for follow-up studies. He had no complaints and was feeling fine. The liver was still enlarged, but liver studies were

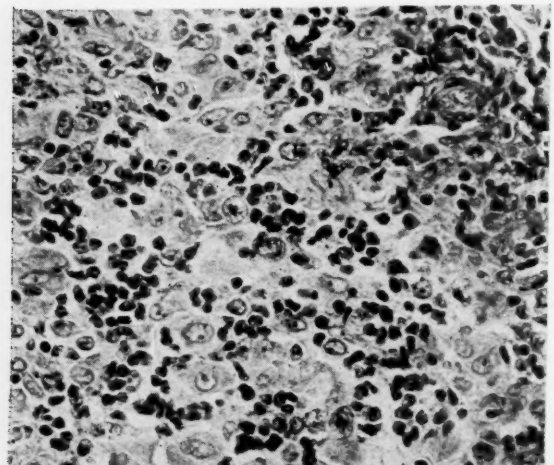

FIGURE 3. *Photomicrograph of the Spleen, Showing the Sarcoid Lesions (x400).*

negative as before. A slight leukocytosis was present, with a normal differential. A tuberculin intradermal test was weakly positive when carried to strong dilutions. The sedimentation rate was elevated to 36 mm. per hour (Wintrobe method). X-ray examination of the chest was negative, except for a slight residual pleural effusion at the left base. X-ray films of the hands were normal. The patient remained afebrile and was discharged after 9 days of hospitalization.

DISCUSSION

This case was apparently one of sarcoidosis that appeared limited to the spleen, causing splenomegaly and selective depression of the red and white cells. The platelets were not involved, and the bone marrow was normoplastic. The criteria of hypersplenism, according to Dameshek,[1] were fulfilled, and the spleen was removed, resulting in the return of the blood picture to normal along with marked clinical improvement. The histopathological studies of the spleen revealed the lesions most consistent with sarcoidosis.

Dameshek[1] and Welch and Dameshek[7] have postulated that the development of the one or more cytopenias in hypersplenism is due to abnormal or excessive splenic activity causing bone-marrow inhibition. Doan,[3] on the other hand, believes that the peripheral blood status is due to increased phagocytosis of the blood-cell elements of the spleen.[2, 8] The syndrome of hypersplenism includes idiopathic thrombocytopenic purpura and congenital and acquired hemolytic anemias, and may be found in the many causes of splenomegaly such as Banti's disease, chronic malaria, tuberculosis, cirrhosis of the liver, Felty's syndrome and leukemia.[1-4, 6-8] The treatment recommended by all advocates of the theory of hypersplenism is splenectomy, which usually relieves the condition.[1-4, 7, 8]

SUMMARY

A case of sarcoidosis of the spleen producing the syndrome of hypersplenism is presented.

The cytopenias and clinical symptoms were relieved by splenectomy.

We are indebted to Dr. Willys Monroe, pathologist at the Norfolk Marine Hospital, for his pathological interpretations and photographs, and to Drs. Charles A. Doan, Philip Custer, Tracy B. Mallory, Wiley Forbus and Paul Klemperer for their interpretations of the slides.

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THE IMPORTANCE OF RECOGNIZING POST-INFARCTIONAL SHOULDER-HAND SYNDROME

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In the past twenty years it has been pointed out by several authors[1-5] that persistent pain of the shoulders, arms and hands follows myocardial infarction. It is not always an index of progressing coronary-artery disease. Persistent pain is due in some cases to the so-called shoulder-hand syndrome, a reflex type of pain resembling causalgia, which may or may not be accompanied by reflex dystrophy of one or both of the upper extremities.

The syndrome has recently been described in detail by Steinbrocker et al.,[6] who divided its clinical course into three stages: Stage I, which consists of a painful shoulder, followed or accompanied by painful, swollen and stiff fingers (there are usually color changes varying from a dusky pink to cyanosis); Stage II, which usually brings some relief of the shoulder pain with a subsidence of the swelling in the hands (however, the stiffness and flexion deformities of the fingers increase, and atrophy of the subcutaneous tissues and intrinsic muscles of the hands occurs); and Stage III, which is characterized by progression of the atrophic changes until a Dupuytren contracture results.

The mechanism of the development of this syndrome is mainly theoretical. Recently, Hilker[7] has added to its present neurophysiologic concepts. He believes that decreased local nutrition resulting from decreased cardiac output, hypotension, forward failure with ischemia and tissue anoxia may act as an active stimulus to the internuncial pool of the spinal cord. The internuncial pool sets up vasospastic responses that lead to the shoulder-hand syndrome.

There is little to add to the clinical description of this entity, and the theories concerning its cause seem adequate. However, it is believed that additional emphasis should be placed on the importance of recognizing this syndrome, especially during Stage I.

The recognition of the shoulder-hand syndrome as a cause of persistent pain after myocardial infarction is of the utmost importance for several reasons. In the first place, it must be considered so that excessive weeks of bed rest can be avoided. Any pain in the shoulders, arms and hands after an acute myocardial infarction is rightfully viewed with suspicion. However, persistent pain in these areas is often accepted as sufficient evidence to require many extra and needless weeks of bed rest far beyond the usual period for these patients. Secondly, this syndrome must be remembered so that expensive and valueless procedures can be avoided. The shoulder-hand syndrome on physical examination may resemble bursitis, arthritis and the scalenus-anticus syndrome. The treatment for the latter conditions is of little or no value in the management of the shoulder-hand syndrome. Finally, a patient who has had a myocardial infarction has been sufficiently impressed by the seriousness of his illness, and, when pain continues and unless the shoulder-hand syndrome is recognized, the physician may help the patient superimpose a severe cardiac neurosis on coronary-artery disease.

Two cases are presented to emphasize the importance of the recognition of this syndrome after myocardial infarction.

Case Reports

Case 1. Mrs. W. W., a 55-year-old housewife, was first seen on June 6, 1949, because of moderate substernal pain. For about 1 month she had had "indigestion" consisting of belching and fullness in the epigastrium. On the day she was first seen the epigastric fullness had become more severe and was accompanied by substernal pain. The past history was essentially irrelevant except for pelvic operations in 1935 and 1942. There was no history of hypertension.

Physical examination revealed a markedly anxious woman with moderate dyspnea and slight cyanosis of the lips. The apical heart rate was 130, and the blood pressure was 150/90. The examination was otherwise negative except for lower abdominal incisional scars.

An electrocardiogram was interpreted as consistent with probable myocardial infarction.

The patient was treated symptomatically. After 1 month she was allowed up in a chair for short intervals, with bathroom privileges. After several days moderately severe pain in the left shoulder developed. Complete bed rest was again advised. She became quite concerned about herself, almost to the point of hysteria. After another month with no clinical or electrocardiographic changes she was allowed up again. The shoulder pain increased. Weakness and tingling sensations in the left hand developed. It was noticed that the skin of the left palm appeared bound down to the flexor tendons. A neurosis was firmly fixed. She became depressed, cried a great deal and in general kept the entire family upset.

About 3 months after the infarction the left shoulder became stiff, and pain was especially severe on internal rotation and abduction of the arm. Pressure applied over the shoulder caused the patient to cry out. She was unable to abduct the arm more than 45°. An x-ray film of the shoulder was normal. She received x-ray therapy and diathermy without relief. Several abscessed teeth were extracted. Salicylates were administered.

About 12 months after the infarction the shoulder stiffness with slight pain remained. There was weakness and tingling of the left hand. The neurosis had improved somewhat with reassurance and explanation of the pain.

This case illustrates the significance of remembering this syndrome after myocardial infarction for three reasons. Firstly, in retrospect the patient was probably kept in bed several weeks more than was necessary. This was done purely because of pain in the left shoulder. This extra bed rest was

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probably of no value but undoubtedly increased the symptoms by imposing disuse atrophy on the reflex syndrome. Fibrosis occurs about a joint that is long in disuse.[8] Joint and bone atrophy will follow. Johnson,[9] who reported 39 cases of this syndrome, believed that the shoulder symptoms were entirely due to voluntary and involuntary splinting of the shoulder by the patient because of fear of an anginal attack. Steinbrocker et al.[6] believe the shoulder and hand symptoms are all of the same vasospastic origin. Whether the shoulder symptoms are due entirely or in part to reflex vasospasm, it seems logical that disuse would aggravate the condition, and prolonged bed rest is certainly conducive to disuse of the extremity. In addition, the prolonged bed rest led to anorexia, restlessness and constipation in this patient. Anyone who has undergone the rigors of the bedpan for more than a month will readily agree that for this single reason extra and needless bed rest is to be condemned.

Secondly, inappropriate therapy was instituted in this patient because the syndrome was not recognized. She was treated with diathermy and x-rays, and several abscessed teeth were extracted. Some authors[1, 10] advocate physiotherapy, especially diathermy. However, this patient and 4 others treated with diathermy were not relieved, and some believed the pain was increased by the diathermy. Edeiken and Wolferth[2] found physiotherapy of no value and x-ray therapy of doubtful value in the treatment of this syndrome. Abscessed teeth should be extracted regardless of their effect on the syndrome. However, it was believed that this patient was not helped by the procedure. The removal of foci of infection seemed to be of no benefit in Askey's[5] series. The appropriate therapy of this syndrome is not in the scope of this paper, but paravertebral sympathetic infiltration with procaine, stellate and upper-dorsal-ganglion blocks, brachial-plexus block, sympathetic surgery and the use of tetraethyl ammonium salts are recommended by Steinbrocker.[6] Recently, Traut[10] has suggested the use of Priscoline.

Finally, because the syndrome was not recognized at first a severe cardiac neurosis that was more disturbing to the patient and her family than the primary disease developed. She was literally afraid "to move a finger." It is believed that this could have been avoided if the true cause of the pain could have been explained to her. Later, when the syndrome was explained the neurosis improved. This patient had a justifiable reason for the development of the neurosis since she had organic heart disease. But, as White and Glendy[11, 12] have pointed out a cardiac neurosis is more difficult to treat than the heart disease itself.

CASE 2. C., a 48-year-old miner, was admitted to a nearby neuropsychiatric hospital on August 29, 1949, with the provisional diagnosis of psychoneurosis. His chief complaint at this time was "drawing" sensations and pain in his shoulders, arms and hands. There were also burning sensations in the axillas. The past history revealed that 18 months previously he had "fallen out" while at work; at a hospital the diagnosis of myocardial infarction had been made. About 1 year later he had a similar episode, and the diagnosis of infarction was again made. The shoulder, arm and hand symptoms began soon after his initial attack and continued until the present admission.

Physical examination revealed generalized arteriosclerosis. The chest was emphysematous. The pulse was 100, and the blood pressure was 180/120. The heart was normal in size and rhythm. There were no murmurs. The hands were drawn in flexion, and the skin over the hands was cold and moist.

An electrocardiogram revealed a left-bundle-branch block. Urinalysis was normal except for a + test for albumin. A complete blood count was not done.

This case speaks for itself. Although the patient had progressed to Stage III of the shoulder-hand syndrome the shoulder and hand pain had not been recognized, and he had been regarded as a psychoneurotic. He had some neurotic characteristics, but they were based primarily on the shoulder-hand symptoms.

SUMMARY

Two cases illustrating the seriousness of the misdiagnosis of the shoulder-hand syndrome after myocardial infarction are presented. Stage I of this syndrome is often diagnosed by symptoms alone, and these symptoms might easily be attributed to coronary-artery disease unless that syndrome is kept in mind. However, when Stage III of the syndrome is reached the diagnosis is still sometimes not made. The recognition of this condition is important in order to avoid needless bed rest and inappropriate therapy. But more important than these reasons is the fact that a severe cardiac neurosis that is very troublesome and difficult to treat may develop.

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MEDICAL PROGRESS

LABORATORY DIAGNOSIS OF POLYCYTHEMIA AND ANEMIA*

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1. Diagnostic Problem in Polycythemia and Anemia

Diagnosis of Polycythemia

The presence of polycythemia may be suspected from the appearance of the patient or detected readily by determination of the hemoglobin or hematocrit of peripheral blood. The physician will usually be able to recognize, from the history and physical examination, whether polycythemia results from loss of plasma or from hemoconcentration, or is related to a condition producing arterial anoxia (Table 1). If there is a normal arterial oxygen saturation in the presence of polycythemia, the clinical problem is more complex, requiring the recognition of such conditions as an early phase of leukemia or early myeloid metaplasia. The diagnosis of polycythemia vera is made largely by excluding known causes for polycythemia. The establishment of the etiology of the polycythemia is of importance in determining the proper treatment, since the polycythemia of arterial anoxia may respond poorly to a lowering of the hemoglobin content of peripheral blood, a procedure that brings benefit in polycythemia vera.[1-4]

Frequency of Anemia

The finding of anemia is a frequent observation in clinical medicine. For example, approximately 10 per cent of women have moderate hypochromic anemia caused by blood loss or deficiency in iron during the period of puberty and childbearing, and until the menopause.[5] Also, anemia is a frequent complication of other diseases such as chronic infection, liver disease, nephritis, neoplastic disease, lymphoma and leukemia.

As an illustration of clinical evidence of anemia, Sturgis[6] reports the following. In about 25,000 routine admissions of patients over fourteen years of age to inpatient and outpatient departments, an anemia of clinical significance was observed in 1 of every 8 patients (12 per cent). Of these, the most frequently observed (41 per cent) was a normocytic, normochromic type, usually due to chronic infection and less commonly to chronic nephritis. Next in frequency (39 per cent) was a microcytic, hypochromic anemia due to iron deficiency that is most frequently associated with chronic hemorrhage. The remaining group (20 per cent) included, for the most part, patients with myelophthisic anemia in association with various conditions such as leukemia, Hodgkin's disease and different types of cancer, and with the macrocytic anemias such as pernicious anemia, refractory anemias and the hemolytic anemias.

TABLE 1. *Etiology of Polycythemia Based on Physiologic Mechanisms as Modified from Castle[1] (the Mechanisms of the Third Group Have Not Been Established and Are Suggested As Theoretical Possibilities).*

1. *Transient (Relative) Polycythemia*
Loss of plasma: thermal injury, crush injury
Hemoconcentration (dehydration): vomiting, diarrhea, diuresis, excessive sweating, water deprivation
2. *Polycythemia from Arterial Anoxia — Secondary Polycythemia*
Low oxygen tension in inspired air: high altitude
Fetal circulation in utero
Heart disease: congenital anomalies with mixing of venous with arterial blood
Disease of the lungs: emphysema, chronic bronchitis (Ayerza's syndrome), tuberculosis, fibrosis, silicosis, cavernous hemangioma, pulmonary arteriovenous fistula, pulmonary congestion from left heart failure
Changes in hemoglobin: chronic carboxyhemoglobinemia, chronic methemoglobinemia
3. *(Theoretical) Anoxia of Erythropoietic Tissue*
Histotoxic anoxia
Administration of cobalt (? cobalt-oxygen-cysteine complex)
Stagnant anoxia
Fibrosis of capillaries
? Fibrosis of bone marrow
? Hypertension
? Cushing's syndrome
Competitive anoxia: increased leukopoiesis in bone marrow
Early benzol (benzene) and radium poisoning
Early leukemia and nonleukemic leukopoiesis
Polycythemia vera

Therapeutic Importance of the Physiologic Classification of Anemia

Once an anemia is detected by screening examinations, the physician should proceed to classify it into one of the three broad physiologic groups, shown in Table 3, before attempting to make a specific or etiologic diagnosis of a particular dis-

*Adapted from *A Syllabus of Laboratory Examinations in Clinical Diagnosis* (in press), by permission of the Harvard University Press.

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ease or anemia. The anemia can usually be classified with reliability by obtaining a limited number of data by relatively simple examinations, as outlined below in Section 5. The practical importance of classifying an anemia correctly is immediately apparent from the difference in the *treatments* that are indicated for the three major classes of anemia.

For example, in *acute* and *subacute blood loss*, the major problems are to prevent death from blood loss itself, to stop the hemorrhage and to restore the blood volume and hemoglobin level to normal. This is done by transfusions as indicated, by hemostasis and usually by administration of iron during the recovery period. In most cases there is no indication for the use of liver extract, vitamin B_{12} or folic acid.

In the *hemolytic anemias* as a group, there is *no* apparent benefit from the administration of iron,

TABLE 2. *Morphologic Characteristics of Red Cells As Related to Diagnosis of Certain Anemias.*

VARIETY OF ANEMIA	SIZE		SHAPE	CONTENT OF HEMOGLOBIN		IMMATURE FORMS	
	AVERAGE (MCV)	VARIATION	VARIATION	AVERAGE MCHC, MCH	VARIATION	RETICULOCYTES	NUCLEATED RED CELLS
Blood loss Acute and subacute blood loss without iron deficiency.	Usually the MCV is normal or slightly elevated with the appearance of new young polychromatophilic macrocytes (reticulocytes). Variation in size is only moderate.		The cells have normal shape with only moderate variation in shape.	In the absence of iron deficiency, the hemoglobin content (MCH) and concentration (MCHC) are normal.		Reticulocytes vary with the degree of anemia and the time after the hemorrhage. Nucleated red cells may occur after acute, severe hemorrhage.	
Hemolytic Anemias (see Table 3 for the general changes in peripheral blood and Table 4 for anemias omitted from this classification).							
Acute hemolytic episode without anemia	In paroxysmal cold hemoglobinuria, an episode of hemoglobinemia and hemoglobinuria may be induced by chilling of an extremity. No anemia develops because the number of red cells destroyed is small. In this instance, *the morphology of red cells is normal.*						
Severe acute hemolytic anemia Incompatible transfusion reaction Intoxication by drugs or chemicals Thermal injury	During the acute increased blood destruction, the MCV is normal. With the appearance of young red cells, the MCV may be slightly elevated.		The shape and hemoglobin content are usually normal. The red cells show marked fragmentation, however, in naphthalene poisoning and thermal injury. Heinz–Ehrlich bodies occur in many cases of intoxication by drugs and chemicals.			A response of reticulocytes and nucleated red cells occurs regularly and depends upon the severity of the anemia.	
Chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria	The MCV may be normal or increased to values as high as 120 u^3. There is moderate variation in size.		Moderate variation	Normal		Chronic reticulocytosis, range 3 to 19 per cent	Usually absent
Chronic acquired hemolytic anemia (red cells agglutinated in Coombs test)			There is moderate variation in shape. Occasionally spheroidal red cells are seen when the osmotic fragility is increased.	Normal		The chronic reticulocytosis varies with the severity of the anemia but may be as high as 20 to 40 per cent for months. Nucleated red cells are seen in severe anemia.	
Congenital hemolytic jaundice (hereditary spherocytosis)	The MCV is usually normal. There is moderate variation in size.		Moderate variation in shape. Small round spherocytes are usually present, and are characteristic of the condition.	The hemoglobin concentration is usually normal. Spherocytes, by virtue of their increased thickness, appear "hyperchromic" on the blood film.		Chronic reticulocytosis is characteristic. Usually the levels are 5 to 10 per cent but may be 15 per cent or higher. Reticulocytosis may occur *without* anemia. Nucleated red cells occur with severe anemia.	
Sickle-cell anemia	The MCV is usually normal; occasionally it is slightly microcytic. However, the red cells are thin and flat and consequently have a larger diameter than normal. This gives an appearance of macrocytosis on the film.		Permanently sickled forms, target cells, oat-shaped and pencil forms may be seen on the film.	Normal or moderately decreased	Target forms appear as large cells with variable hemoglobin.	Reticulocytosis occurs with chronic anemia — range 2 to 22 per cent.	Increased markedly in hemolytic crisis
Cooley's anemia (Thalassemia major)	Microcytosis	*Extreme* variation	The most *extreme variation in shape* occurs in this disease	*Extreme hypochromia*	*Extreme variation*	Chronic reticulocytosis	Usually present
Anemias Due to Decreased Production of Red Cells (see Tables 3 and 4 for comments on mechanism and listing of specific diseases omitted from this classification).							
Pernicious anemia (a) Remission (no anemia)	Normal		Normal	Normal		Normal	
(b) Moderate anemia	Moderate *macrocytosis*	Moderate variation	Moderate variation in shape	The MCH is moderately increased; MCHC normal, variation only moderate.		Normal	
(c) Severe anemia	*Extreme macrocytosis* to an MCV of 150 u^3 or higher	*Extreme variation*	*Extreme* variation with oval macrocytes, microcytes, tail forms	The MCH usually is *extremely* elevated owing to the increase in size of the cells; MCHC normal; variation moderate in hemoglobin content.		The reticulocytes are decreased in absolute number. There is an occasional nucleated red cell.	
Chronic iron deficiency				Both the MCHC and MCH are moderately decreased with moderate variation in hemoglobin content		Normal	
(a) Moderate	Moderate microcytosis	Moderate variation	Moderate variation in shape, pencil forms				
(b) Extreme	*Extreme microcytosis*	*Extreme variation*	*Extreme* variation in shape with microcytes, pencil forms, tail forms	Both MCHC and MCH are *extremely low.* The variation in hemoglobin content of cells is *extreme.*		The number of reticulocytes is usually *low*, but there may be occasional nucleated red cells.	

liver extract, vitamin B_{12}, folic acid or vitamin C, but there may be indications for splenectomy or transfusions or both.

In the *anemias due to decreased production of red cells*, the response to therapeutic agents is *specific* and of benefit only in cases with a deficiency. Liver extract, vitamin B_{12} and folic acid will not be effective except in such conditions as the nutritional macrocytic anemias and will not be effective in be made for a considerable period, and the physician may be required to base the prognosis and treatment of the patient on the physiologic classification.

For example, subacute blood loss may be suspected many weeks before it is possible to find evidence for bleeding or the cause of the bleeding. The manifestations of hemolytic anemia may be clearly established, and many of the specific hemolytic anemias may be excluded by the tests outlined

TABLE 3. *Classification of Anemia Based on Physiologic Activity of Bone Marrow (Modified from Castle and Minot[7]).*

	BONE MARROW PHYSIOLOGICALLY HYPERACTIVE ALWAYS HYPERCELLULAR		BONE MARROW PHYSIOLOGICALLY HYPOACTIVE HYPOCELLULAR TO HYPERCELLULAR*
VARIETY OF ANEMIA	ACUTE AND SUBACUTE BLOOD LOSS OF INTERNAL HEMORRHAGE *without deficiency of iron*	HEMOLYTIC ANEMIAS WTIH INCREASED DESTRUCTION AND INCREASED PRODUCTION OF RED CELLS	ANEMIAS WITH DECREASED PRODUCTION OF RED CELLS
	The *stimulus* for production of hemoglobin is the same in all anemias — decreased oxygen content of the blood		
Red cells Reticulocytes Nucleated RBC MCV MCH MCHC	After acute hemorrhage, there is no immediate change in the red cells. Reticulocytes appear in a day or two and reach maximum concentration in 3–6 days, at which time the size (MCV) of the red cells is increased. In subacute hemorrhage, there may be continuing moderate reticulocytosis with normal MCV or slight macrocytosis. In the absence of deficiency of iron, the hemoglobin indexes are normal.	In chronic hemolytic anemias, there is continuing reticulocytosis with normal or increase in size (MCV) and normal hemoglobin content (MCH, MCHC), except for Cooley's and sickle-cell anemia. In acute hemolytic anemia, there may be a moderate or marked increase in nucleated red cells. For specific abnormalities of red cells, see Table 8 in the second part of this report. In acute infection complicating chronic hemolytic anemia, there may be a transient aplasia of erythropoiesis with absence of reticulocytes.[8]	The red-cell indexes are high in anemias due to deficiency of liver extract and low in anemia due to iron deficiency. In the other anemias the indexes are normal, or there is moderate macrocytosis. Reticulocytes are usually low or normal in number and nucleated red cells are absent except in myelophthisic anemia, in which reticulocytes and nucleated red cells are increased in a variable manner.
White cells Total number Myeloid response Atypical cells	The first sign of acute hemorrhage may be leukocytosis and increased granulocytes with variable myeloid response. In subacute blood loss the white cells are usually normal.	In acute hemolytic anemia, there may be a marked leukocytosis and extreme myeloid response. In chronic hemolytic anemia, the white cells may be normal. In paroxysmal nocturnal hemoglobinuria there is leukopenia.	In anemias due to nutritional deficiency, there is frequently leukopenia, relative lymphocytosis and an increased maturity of the neutrophils. In aplastic anemia, there is leukopenia. In myelophthisic anemia, there may be pancytopenia, myeloid response or manifest leukemia.
Platelets	Platelets increase immediately after hemorrhage.	In most acute or chronic hemolytic anemias, the platelets are normal or increased. In paroxysmal nocturnal hemoglobinuria, there is moderate thrombocytopenia.	There is thrombocytopenia in pernicious and aplastic anemia, and extremely variable degrees of thrombocytopenia in toxic, physical, and mechanical involvement of bone marrow.
Bilirubin metabolism	In blood loss, the bilirubin of plasma and excretion of fecal urobilinogen are low. With hemorrhage into viscera, there may be mild jaundice.	In acute and chronic hemolytic anemia, there may be increased bilirubinemia with high fecal urobilinogen; or there may be hemoglobinemia, methemalbuminemia, hemoglobinuria and hemosiderinuria. In chronic hemolytic anemia, there may be no increase in bilirubinemia, but a significant increase in fecal urobilinogen.	In iron-deficiency anemia, the plasma bilirubin and fecal urobilinogen are low. In pernicious anemia, they may be significantly elevated. There are variable elevations in bilirubin in other anemias in which there is an increase in the rate of destruction of red cells or disease of the liver.
Therapeutic response	In the absence of iron deficiency, blood regeneration will proceed at a normal rate. Otherwise, iron therapy is indicated. There is no indication for administration of liver extract, vitamin B_{12} or folic acid. Transfusions are used to restore the decreased blood volume.	Splenectomy and transfusion are used in selected cases. There is no response to iron, liver extract, vitamin B_{12} or folic acid, but a therapeutic trial may be indicated if the diagnosis is in doubt.	Liver extract, vitamin B_{12}, folic acid, iron and thyroid replace specific deficiencies and are not effective when there is no deficiency. Irradiation or chemotherapeutic agents may be used in lymphoma and leukemia. Transfusions may be necessary to support life.

*The bone marrow may appear hypercellular when the peripheral blood shows anemia, leukopenia and thrombocytopenia. There may be poor correlations with the cellularity of the bone marrow and the findings in the peripheral blood.[1]

the anemia of iron deficiency or in many other types of anemia.

Diagnosis of Etiology or Variety of Anemia

In a systematic scheme of proceeding from the simpler to the more complex procedures, the physician first detects the presence of the anemia and then classifies it on the basis of the physiologic activity of the bone marrow. This is done before he embarks on the larger number of more demanding laboratory procedures that may be required to establish the diagnosis of a particular variety of anemia. In some cases a specific diagnosis cannot in Section 4 without establishing the etiology or an exact diagnosis. Similarly, an anemia resulting from decreased production of red cells may exist for a considerable period before its cause is apparent in such conditions as aleukemic leukemia or metastatic infiltration of the bone marrow.

However, considerable advance has been made in the diagnostic accuracy of laboratory procedures. Thus, in the group of hemolytic anemias, a series of screening examinations are available for detecting abnormalities of the red cells, the presence of antibodies in the serum and abnormalities of hemoglobin catabolism. Also, splenectomy may be in-

dicated in hemolytic anemia, even though the exact cause of the disease is unknown. In anemias resulting from decreased production of red cells, special examinations may be diagnostic of the cause of the disease, as in the use of liver extract in pernicious anemia and the biopsy of bone marrow in neoplastic disease. In chronic infection, however, the existence of anemia may be correlated with the infection without knowledge of the mechanism of the anemia.[9-11]

2. Physiology of the Normal Level of Hemoglobin

The red blood cell serves as a small package for the transport of the protein hemoglobin, which has the remarkable property of combining with oxygen to such a degree that each gram of hemoglobin carries approximately 1.34 ml of oxygen gas when fully saturated. It is probable that the oxygen tension of the bone marrow itself is the factor that

Table 4. *Classification of Particular Anemias, with Comments on Etiology, Diagnostic Characteristics and Mechanism.*

1. *BONE MARROW PHYSIOLOGICALLY HYPERACTIVE*

(1) *Acute and Subacute Blood Loss* (without iron deficiency) (see Table 3).

(*a*) Hemorrhage, external.

(*b*) Hemorrhage, internal.

(2) *Hemolytic Anemias — Increased Destruction and Production of Red Cells.*

(*a*) *Congenital and Hereditary Defects of Red Cells.*

(i) *Congenital Hemolytic Jaundice.*[8, 15-28] Congenital hemolytic jaundice, or hereditary spherocytosis, is a familial disease, transmitted as a mendelian dominant, that may not be manifest clinically or show any anemia (see Fig. 6 in the second part of this report). Anemia may be mild or severe with variable degrees of jaundice. The trait is characterized by the presence of abnormally spheroidal red cells. The mechanical fragility of the red cells is increased but the osmotic fragility may be increased or normal. On incubation for 24 hr. at 37.5°C. the osmotic and mechanical fragilities of the red cells increase markedly for patients with or without anemia and before or after splenectomy. Splenectomy apparently removes an organ for segregation and destruction of red cells and results in symptomatic cure, but the abnormalities of the red cells remain.

(ii) *Sickle-Cell Anemia.*[29-46] Although 6 to 8 per cent of Negroes (rarely white persons) have the sickle-cell trait, only about 1 in 40 with the trait has anemia. Cells are sickled by removal of oxygen from hemoglobin. Sickled cells have an increased viscosity of flow in capillary tubes and increased mechanical fragility. These effects may be related to the incidence of thrombosis and destruction of red cells in the patient.[18, 38]

Neel[45] has demonstrated that patients with the sickle-cell trait are heterozygous "carriers" of an abnormality that occurs without symptoms in from 4 to 11 per cent of Negroes. Pauling et al.[46] have demonstrated that patients with the sickle-cell trait have a *mixture* of normal and defective (sickling) hemoglobin that requires a low oxygen tension to sickle.[40] However, patients with sickle-cell anemia are homozygous[46] and have 100 per cent defective (sickling) hemoglobin,[46] which sickles completely at a higher oxygen tension[40] than occurs with the hemoglobin (mixture) from the sickle-cell trait. The ratio among Negroes of those with the sickle-cell trait (heterozygous) to those with sickle-cell anemia (homozygous) is approximately 40:1.[29-44] Patients with sickling of the red cells may be classified as having the sickle-cell trait, if there is no anemia, and as having sickle-cell anemia if a hemolytic anemia is present.

(iii) *Cooley's Anemia (Thalassemia Major).*[3, 46, 47] Cooley's anemia is a familial disease characterized by a severe, hypochromic, microcytic anemia with nucleated red cells and chronic reticulocytosis in the peripheral blood. There is moderate variation in size and marked variation in shape of the red cells, with bizarre forms and stippled cells. The disease does not respond to treatment with iron. The red blood cells are decreased in osmotic fragility, but their mechanical fragility is normal.

(iv) *Cooley's Trait (Thalassemia Minor).*[3, 46, 47] This is a mild and variable condition often confused with hypochromic anemia due to iron deficiency. It is a familial abnormality inherited as a trait from one affected parent. This is in contrast to Cooley's anemia, which is inherited, apparently from both parents, who are both affected by the Cooley trait. There may be only minor changes in the red cells, or there may be an abnormally elevated red-cell count, a decrease of hemoglobin and a definite microcytic anemia.

(*b*) *Acquired Defects of Red Cells.* The diseases listed below in paragraphs (*d*), (*e*), (*f*) and (*g*) could also be classified as resulting from acquired abnormalities of the red cells. Many aspects of the classification are arbitrary.

(i) *Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria.*[48-51] This is a chronic hemolytic anemia with continuing intravascular hemolysis, variable hemoglobinemia, chronic methemalbuminemia, variable hemoglobinuria and chronic hemosiderinuria. In vitro, the patient's red cells are hemolyzed by acidified serum from the patient or normal subjects. Hemolysins have not been found in the patient's serum. The red cells have normal osmotic and mechanical fragilities. The cause of the disease is unknown. In vivo increased hemolysis occurs during sleep, apparently resulting from a slight decrease in pH.

(ii) *Acute Hemolysis with Thermal Burns.*[52-55] Heating of red cells in the range of 50–55°C. causes a progressive subdivision of red cells with increased osmotic and mechanical fragilities. In the burned patient increased destruction of red cells, injured by heating, results in hemoglobinemia, methemalbuminemia, hemoglobinuria and hemosiderinuria. It is frequently associated with lower-nephron nephrosis.

(iii) *Pernicious Anemia.* It has been demonstrated that the survival is abnormally short for red cells obtained from patients with pernicious anemia when transfused into normal subjects. Because normal red cells survive normally in the patient with pernicious anemia, the red cells produced are defective. There is evidence for increased destruction of heme pigment in the patient with pernicious anemia.[52, 56]

(*c*) *Agents Causing Hemolysis in Vitro and in Vivo.*

(i) *Paroxysmal Cold Hemoglobinuria.*[57-59] In this disease, frequently associated with syphilis, chilling of the body produces acute hemoglobinemia and hemoglobinuria. *In vitro* a hemolysin is attached to the red cells on chilling in the presence of serum complement, and hemolysis occurs on warming to room or body temperature. This is the Donath–Landsteiner reaction. Anemia occurs only transiently after acute hemolytic episodes.

(ii) *Hemolysin in Acquired Hemolytic Jaundice.*[40, 41] (See paragraph *d*, iii).

(iii) *Venom Poisoning.*[60] The venoms of certain reptiles and arachnids produce hemolysis in vivo and in vitro.

(*d*) *Hemolytic Anemias Associated with Abnormal Agglutination of Red Cells.* A variety of hemolytic anemias are associated with abnormal degrees of agglutination of red cells, which may be related to their increased destruction in vivo. Hemolysins are not necessarily demonstrable.

(i) *Hemolytic Transfusion Reactions.*[8, 14, 61] Incompatibility of blood may result from administration of red cells that are agglutinated by anti-A, anti-B or anti-Rh antibodies, or from the administration of anti-A or anti-B agglutinins to a recipient who is Group A, B or AB. Isohemolysins are absent in about 70 per cent of Group A and B incompatibilities. Anti-Rh antibodies are agglutinins and not hemolysins.

governs the level at which the hemoglobin (or the oxygen-carrying power) of the blood stream is maintained. In the normal adult the volume of circulating red blood cells, exclusive of the plasma, is approximately 2000 ml or a volume and weight exceeding considerably the size and weight of the liver. This volume of red cells contains roughly 600 gm of hemoglobin, which will carry 800 ml of oxygen.

In the normal subject there is such a delicate balance between the processes of production and destruction of red cells and of hemoglobin that the number of erythrocytes and the concentration of hemoglobin in the blood stream remain remarkably constant during life.[1] It is estimated that the normal life of the red blood cell is approximately a hundred to a hundred and twenty days,[12-14] indicating a daily destruction and replacement of about 1 per cent of the red-cell population, or the red cells derived from about 40 ml of whole blood, which is equivalent to the loss of about 6 gm of hemoglobin per day. The evidence for blood *destruction* in the

TABLE 4 (*Concluded*).

(ii) *Erythroblastosis Fetalis.*[1, 64-66] Anti-Rh agglutinins from the maternal blood gain access to the fetal circulation and are incompatible with the Rh+ blood of the fetus. Hemolysins are not demonstrable.

(iii) *Acquired Hemolytic Jaundice.*[1, 15, 17, 19, 21, 60, 61, 67-77] Acute or chronic hemolytic anemia may occur without known cause or in association with such conditions as lymphoma or leukemia. In certain of these anemias the red cells show agglutination by the direct Coombs test. The mechanical and osmotic fragilities may be normal or increased. Hemolysins are demonstrable occasionally. The serum usually contains a panagglutinin effective at an acid pH of 6.5 and inactive at pH 8.0. The indirect Coombs test usually shows agglutination if the serum is acidified to pH 6.5 but may show none if the pH of serum is 8.0. A hemolysin active at pH 7.0 and inactive at pH 8.0 has been described.[60] The spleen of these patients shows agglutination of red cells from the pulp and renders normal cells agglutinable by Coombs serum. Hemoglobinuria from chilling occurs in occasional patients with high concentrations of cold autohemagglutinin but with a negative Donath-Landsteiner reaction.[71, 78]

(*e*) *Infections of the Blood Stream.*[1, 7, 66, 79]

(i) *Bacterial Infections.* Infections with such organisms as the hemolytic streptococcus and *Bacillus welchii* (*Clostridium perfringens*) may produce increased destruction of blood.

(ii) *Oroya Fever* (*Carrión's Disease*). The infection of the red cell with *Bartonella bacilliformis*, a rickettsia-like organism endemic in Peru, produced severe hemolytic anemia with hemoglobinemia and hemoglobinuria.

(iii) *Malaria.* Increased destruction of red cells, possibly because of their increased mechanical fragility, occurs with infestation of the red cells with malarial parasites.

(*f*) *Chemical Intoxication.*[1, 63, 80-83] Acute or chronic hemolytic anemia may be caused by such compounds as phenylhydrazine, sulfonamides, naphthalein, certain oxidant compounds such as methylene blue and para-aminophenol, arsine and aniline compounds. The red cells may show increase in osmotic and mechanical fragility and changes in the pigment hemoglobin.

(*g*) *Unknown Mechanisms.*

(i) *Favism.*[84] Acute hemolytic anemia with hemoglobinuria may occur from ingestion of the fava or horse bean (*Vicia faba*) by "sensitive" persons.

(ii) *Anemia in Disease of the Liver.* In certain cases of liver disease, especially alcoholic cirrhosis, there is evidence that there is increased destruction of red cells.

2. *ANEMIAS ASSOCIATED WITH PHYSIOLOGICALLY HYPOACTIVE BONE MARROW: DECREASED PRODUCTION OF RED CELLS*

(1) *Nutritional Deficiency.*

(*a*) *Deficiency of Anti-Pernicious-Anemia Principle.*[1, 7, 85, 86]

(i) *Deficiency of Food* (*Extrinsic*) *Factor.* A diet deficient in substances associated with animal protein may produce a macrocytic anemia responding to food, purified liver extract, vitamin B_{12} or folic acid.

(ii) *Deficiency of Gastric* (*Intrinsic*) *Factor.*[1, 86] In Addisonian pernicious anemia with achylia gastrica, in infestations with the fish tapeworm as seen in Finland and in certain cases of pregnancy there is lack of intrinsic factor. Pernicious anemia responds to purified liver extract, vitamin B_{12} and folic acid. The macrocytic anemia of pregnancy may fail to respond to purified liver extract and vitamin B_{12} but may respond to folic acid.[87, 88]

(iii) *Intestinal Factors.*[1, 89] Macrocytic anemia may occur owing partly to defective intestinal absorption in sprue, steatorrhea and celiac disease and in short circuits of the bowel. The anemia responds somewhat variably to purified liver extract, vitamin B_{12} and folic acid.

(*b*) *Deficiency of Wills's Factor.*[90, 91] Defective diets may cause macrocytic anemia of the tropics and of pregnancy. The anemia may fail to respond to purified liver extract or vitamin B_{12}, but responds to crude liver extract or to folic acid.

(*c*) *Deficiency of Iron.*[92-94] Hypochromic, microcytic anemia due to deficiency of iron may result from inadequate intake during growth or pregnancy, increased loss of blood from menstruation or hemorrhage, or decreased absorption due to gastric anacidity or diarrhea.

(2) *Endocrine Deficiency.*[95] Insufficiency of thyroid or pituitary hormones may be associated with moderate degrees of anemia. More severe anemia may indicate an additional deficiency of liver-extract principle or of iron.

(3) *Toxic Inhibition of Blood Production.*

(*a*) *External Agents.*[1, 8, 96, 97] Benzol (benzene), arsphenamine, lead and insecticides are examples of compounds that have been associated with varying degrees of functional hypoactivity of the marrow. Morphologically, the bone marrow may be hypoplastic or hyperplastic.

(*b*) *Internal Agents.* Chronic infections[8, 10] and renal failure with azotemia[98] are usually associated with anemia with mild hypocellularity of the bone marrow.

(4) *Physical Injury.*
Radiation. Radiation by x-rays, radium or radioactive phosphorus produces variable degrees of aplasia or fibrosis of the bone marrow.

(5) *Mechanical Interference.*

(*a*) *Inadequate Marrow Capacity.*[1, 99] Anemia of the newborn and prematurity develops after the rise in oxygen in the blood when respiration begins.

(*b*) *Myelophthisis.*[8] Anemia with variable degrees of reticulocytosis and nucleated red cells, variable leukocytic response and variable thrombocytopenia may occur in such conditions, involving the marrow, as metastatic carcinomatosis, primary xanthomatosis, osteosclerosis, leukemia, granuloma and miliary tuberculosis.

normal subject results from metabolism of the pigment portion of porphyrin molecule of the hemoglobin complex. The iron and globin of hemoglobin are conserved by the body. The porphyrin ring is opened, forming bilirubin, which appears in the plasma and is excreted in bile. There is very little evidence, in the blood stream of the normal subject, for blood *production*. In the normal adult the nucleated red blood cells of the bone marrow are not seen in the peripheral blood. The only immature circulating erythrocytes, which are observed in small numbers, not over 1 per cent, are the so-called reticulocytes, which show a bluish network when stained by the vital dye cresyl blue.

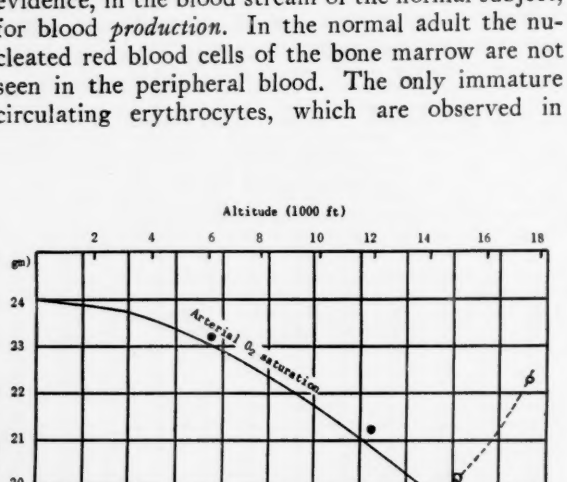

FIGURE 1. *Relation between the Mean Arterial Oxygen Saturation (per cent) and the Mean Hemoglobin Content (gm/100 ml) in Healthy Male Residents at Different Altitudes (Reproduced from Hurtado, Merino and Delgado,[102] with the Permission of the Publisher).*

3. PHYSIOLOGY OF POLYCYTHEMIA

(1) *Terminology*

Although the term polycythemia refers to an increase in the number of red cells, it has been recommended[1] that the term be used only when this increase is accompanied by an abnormal increase in *hemoglobin* since the hemoglobin concentration of whole blood is the physiologically significant finding and to some extent is independent of the size and hemoglobin content of the individual red cells. For example, the hemoglobin may be normal or decreased in the familial disorder of Cooley's trait (Table 4), which is frequently characterized by an abnormally high number of microcytic, hypochromic red cells — a condition that, physiologically speaking, is better classed with the anemias than with polycythemia.

(2) *Transient (Relative) Polycythemia — Plasma Loss or Hemoconcentration*

An abnormal and usually transient increase in the hemoglobin concentration of whole blood may occur when the volume of blood plasma is reduced without loss of red cells — a net decrease in the circulating blood volume. The plasma may be lost from the skin in thermal injury or into the tissues after trauma as in crush injuries of extremities.[100] Hemoconcentration with an increase in plasma proteins may result from loss, largely of water and electrolytes, in conditions producing severe dehydration such as diarrhea, vomiting, diuresis in diabetic acidosis and excessive sweating. In the normal man the spleen is not a significant reservoir organ for red cells[101] as it is in many animals. In cases of marked splenomegaly, however, especially in congenital hemolytic jaundice, a transient increase of hemoglobin of as much as 20 per cent may be produced by shrinkage of the spleen after the injection of epinephrine or at splenectomy.

(3) *Polycythemia from Arterial Anoxia*

A reciprocal relation between the rate of erythropoiesis and the eventual hemoglobin concentration in the peripheral blood, on the one hand, and the oxygen content or saturation of the arterial blood, on the other, has long been recognized in animal experiments. Hurtado[102] has recently demonstrated clearly that normal subjects working at high altitudes show an increase in the hemoglobin concentration of blood that varies inversely with the percentage of arterial oxygen saturation (Fig. 1). In these subjects with increased hemoglobin there is an increase in the blood volume owing to a larger mass of red cells and an increase in the reticulocytes and serum bilirubin, but the leukocytes are *normal*. On return to sea level, there is a gradual return of the hemoglobin level to normal. The results of this fundamental study can be applied to other conditions in which polycythemia results from a physiologic response to arterial anoxia* as observed in the fetus in utero, congenital heart disease, certain cases of acquired heart disease, chronic pulmonary disease, chronic exposure to carbon monoxide (carboxyhemoglobin) and chronic methemoglobinemia.[3, 103]

(4) *Polycythemia Presumably from Anoxia of Bone Marrow*

In polycythemia vera there is a *normal* oxygen saturation of the arterial blood even with a marked increase of hemoglobin. However, the hypothesis has been advanced[1, 104-107] that polycythemia vera

*The term secondary polycythemia is usually applied to this group of conditions. Since polycythemia is, perhaps, always secondary to arterial anoxia, this term has significance only when used to imply oxygen unsaturation of the arterial blood.

may result from a chronically lowered oxygen tension in the erythropoietic cells of the bone marrow produced in one of several ways.

Stagnant anoxia may result from *altered circulation* of blood in the bone marrow as indicated in the observations by Reznikoff et al.[106] of abnormal fibrosis of the capillary walls. Also, it is theoretically possible that the early phases of fibrosis of bone marrow may produce a relative anoxia from poor circulation to the erythropoietic tissue, resulting in stimulation of hemoglobin production. This could account for the transient polycythemia that may precede anemia for various lengths of time in osteosclerosis of bone marrow.

In an observation of Shafer[108] in which dogs were rendered *hypertensive* by section of the cardioaortic and carotid-sinus depressor nerves stagnant anoxia of the marrow may have resulted. A considerable number of animals developed polycythemia that was subsequently reversed by paravertebral sympathectomy. Possibly, a similar mechanism obtains in the polycythemia observed occasionally in Cushing's disease in association with hypertension, and that occurring in cases of subtentorial tumors of the brain, usually with hypertension. In such hypertensive cases, polycythemia may occur without splenomegaly, as described by Gaisböck.[103]

Histotoxic anoxia is possibly the mechanism of the polycythemia in animals[104, 105] and the moderate increase in hemoglobin in normal human subjects[107, 110] that follows the administration of cobalt. The erythropoietic action of cobaltous chloride may depend upon a fundamental alteration of tissue respiration so that erythropoietic tissue may be partially unable to utilize the available oxygen, resulting in a stimulation for production of hemoglobin.[105] Cobalt does not change the oxygen-combining power of hemoglobin.[104]

Castle[1] has further suggested that *competitive anoxia* may occur in the bone marrow in areas of increased leukopoiesis or replacement of bone marrow by a new growth. Accordingly, polycythemia could result, in theory at least, from a sufficiently widespread congenital or acquired increase in the amount of normal leukopoietic tissue so that less oxygen is available to normal erythropoietic tissue. A similar effect might result from an increase in abnormal tissue, such as leukemic infiltration or invasion of the bone marrow by carcinoma or granuloma. In diffuse invasion by abnormal cells, it may be assumed that multiple islands of normal erythropoietic tissue, stimulated by local anoxia, would produce polycythemia as long as the *quantity* of erythropoietic tissue was adequate. With further replacement, however, decrease in the amount of erythropoietic tissue, even though maximally active, would result in a myelophthisic anemia characterized, however, by the finding of increased nucleated red cells and reticulocytes.

4. Physiology of the Anemias

(1) Stimulus for Blood Production

In anemia there is a reduction in the oxygen-carrying substance of the blood as evidenced by a decrease in the concentration of hemoglobin and usually a decrease in the number of red blood cells in the circulation. Anemia results from a failure of the blood-forming bone marrow to maintain a balance between production and destruction of red cells or from blood loss.[1] If the bone marrow is capable of normal production of blood, the *lowered oxygen congent* of the anemic blood will serve as an adequate *stimulus* to the bone marrow for regeneration of hemoglobin and red cells. By means of an increased cardiac output and a greater percentage utilization of the oxygen in the blood, patients may remain comfortably at rest with a hemoglobin and oxygen-carrying power of only one-fifth to as low as one-tenth normal. Because this level serves as a tremendous stimulus to the production of blood by a physiologically active bone marrow, the *absence* of signs of blood regeneration establishes the diagnosis of an abnormally decreased production of red cells (see Table 3).

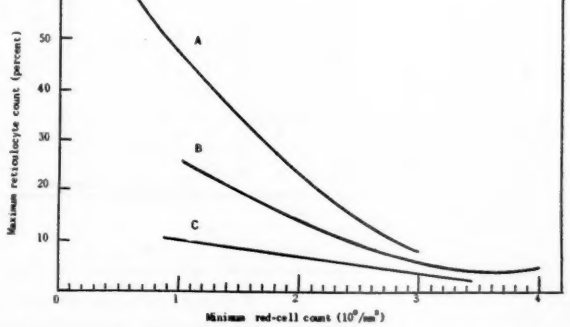

Figure 2. *Reticulocytosis in Pernicious Anemia, Hypochromic Anemia and Anemia after Hemorrhage (Based on Observations of Schiodt*[111]).

Curve A = maximum response in pernicious anemia treated with liver extract.
Curve B = response in hypochromic (iron-deficiency) anemia.
Curve C = response after acute hemorrhage in patients who did not receive iron.

(2) Physiologic Response

If the bone marrow is capable of a normal response to anemia or if a factor is supplied in which the blood-forming organs are deficient, such as iron or liver extract, the processes of regeneration are manifest in the peripheral blood in a reproducible and regular manner. The maximum reticulocyte levels for the response of pernicious anemia to liver extract, of the anemia of iron deficiency to the administration of iron[93, 94, 111, 112] and of the unaided

body to hemorrhage are shown in Figure 2. With extreme regeneration, there appear nucleated red blood cells and reticulocytes in large numbers, with increase in platelets, in white cells and in immature forms of leukocytes. With a mild response, an increase in reticulocytes occurs without nucleated red cells. All gradations between these extremes are observed.

The rate and magnitude of the reticulocyte response to treatment in the anemia of iron deficiency are shown in Figure 3, and compared to the continuing chronic *reticulocytosis* (Fig. 4), which may last a *lifetime* in patients with chronic active hemolytic anemia. It cannot be emphasized too strongly that the bone marrow that is physiologically normal produces red cells and hemoglobin indefinitely at many times the normal rate.

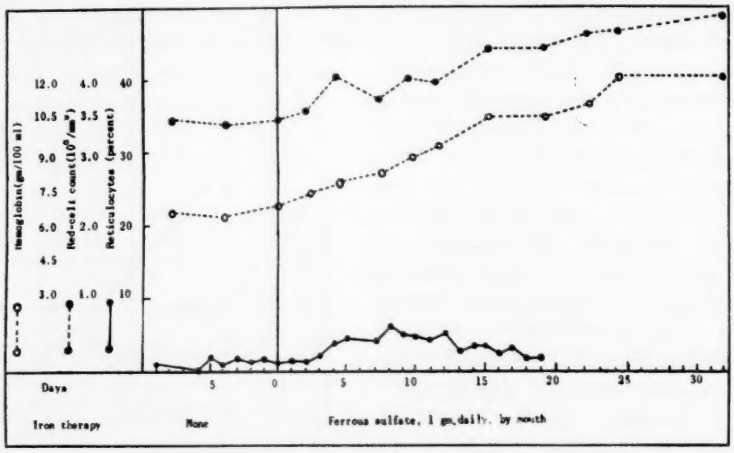

FIGURE 3. *Hypochromic Anemia with Iron Deficiency. Note the moderate but progressive reticulocyte response. The hemoglobin is low for the red-cell count (MCHC = 28 per cent), and the cell size is small (MCV = 68 μ^3).*

(3) *Inhibition of a Physiologic Response*

There is excellent evidence that the physiologic response of the bone marrow may be inhibited by such a factor as infection. Owren[8] has shown the dramatic effect of infection in patients with congenital hemolytic jaundice, who developed an increased anemia associated with a transient *aplasia* of erythropoietic cells of the bone marrow, disappearance of reticulocytes from the peripheral blood, a decrease of serum bilirubin to normal and a rise in serum iron. Spontaneous recovery occurred after the infection, with marked reticulocytosis, leukocytosis, thrombocytosis and a rapid fall in serum iron. This is a classic demonstration of transient inhibition of an overactive erythropoietic bone marrow in hemolytic anemia. Similar results have been observed by others.[25]

Also, in pernicious anemia during active reticulocytosis from liver treatment, an infection may be associated with a cessation of the reticulocytosis and increase of red blood cells in spite of continued therapy until the infection has decreased.[1, 7]

(4) *Physiologic Adjustments*

The oxygen consumption of the body is *not* reduced in anemia, but two important mechanisms provide compensation for the decreased capacity of the blood to carry oxygen. The rapidity and volume of the circulation of blood may be increased, and the percentage of oxygen removed by the tissues from each unit of blood may be greatly increased. There may be no symptoms at rest, but on exertion the patient may note palpitation, tachycardia, dyspnea and weakness. Possibly owing to anoxia, the patient with anemia may also notice easy fatigability, headache, dimness of vision and a tendency to fainting.[101, 113-119]

The adjustment to a mild degree of anemia is so gradual and may be so complete as to escape the notice of the patient and physician. Similarly, it is quite impossible to define the exact level of hemoglobin that permits the diagnosis of anemia to be made. Thus, Wintrobe[3] finds the normal range of hemoglobin in adults to be, for women, 12 to 16 gm per 100 ml and, for men, 14 to 18 gm per 100 ml of blood. It has never been adequately explained why women have a lower "normal" range of hemoglobin concentration than men. It is not known at what level of hemoglobin a given person may have symptoms or signs referable to anemia. Arbitrarily, it can be assumed that, at sea level, an adult is anemic if the hemoglobin is below 12 gm per 100 ml. For some men, however, 12 gm of hemoglobin per 100 ml conceivably may give mild symptoms of anemia; thus, individual variation undoubtedly plays a role in interpretation of the "normal" for

a given subject. Mild anemia may be considered arbitrarily to exist at from 9 to 12 gm of hemoglobin per 100 ml. From 6 to 9 gm of hemoglobin per 100 ml is moderately severe anemia, and 3 to 6 gm per 100 ml is severe. Patients can live without undue discomfort at absolute bed rest with only 2 to 3 gm of hemoglobin per 100 ml — an extreme anemia.

(5) *Classification of Anemia*

A classification of anemia, as modified from Castle[1] and Castle and Minot,[7] based on the physiologic activity of the bone marrow, is shown in Table 3. The clinical features and mechanisms of the anemias are outlined in Table 4. The morphologic characteristics of certain anemias are summarized in Table 2. These tables have the limitations of oversimplification and brevity, but may serve for orientation to some of the known and theoretical mechanisms in anemia. The reader is referred elsewhere[1-3, 5-7, 9-11, 15-21, 62-64, 79, 85-91, 93, 94, 96-99, 112] for more detailed discussions.

5. Diagnostic Examinations for Polycythemia and Anemia

(1) *Screening Examinations*

The screening examinations for the detection and preliminary study of polycythemia and anemia include the procedures usually performed in the initial study of the patient — namely, the history, physical examination, determination of the hemoglobin or hematocrit, white-cell count, differential white-cell count, examination of red cells and platelets on the stained film of blood, and basic examination of the urine and stool.

(2) *Examinations for the Physiologic Classification*

If anemia is present, the following examinations are suggested for the classification of the anemia based on the physiologic activity of the bone marrow (in polycythemia, similar observations are indicated with the additional determination of the oxygen saturation of the arterial blood):

(*a*) Reticulocyte count.
(*b*) Critical re-evaluation of the morphology of red cells on the stained film of blood.
(*c*) Determination of red-cell count, hemoglobin, hematocrit within ± 5 per cent.
(*d*) Calculation of MCV, MCH, MCHC (Wintrobe indexes).
(*e*) Critical differential count of white cells.
(*f*) Estimation of platelets on the stained smear.
(*g*) Determination of plasma icteric index.

From these preliminary data it is possible to judge the degree of polycythemia or anemia, the degree of physiologic activity of the bone marrow,

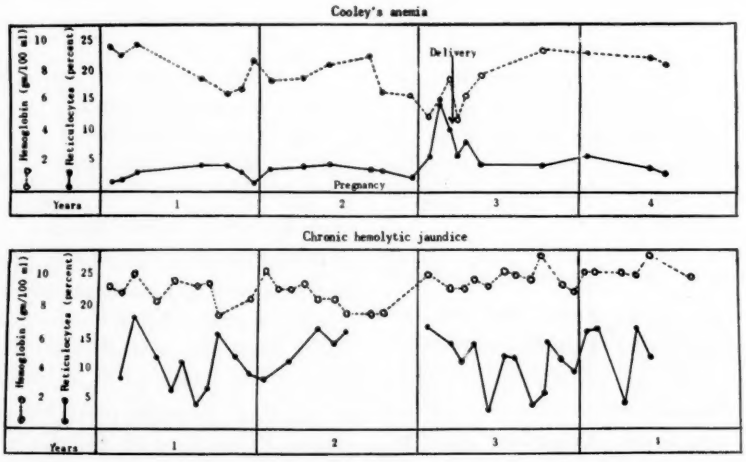

FIGURE 4. *Chronic Reticulocytosis in 2 Patients with Chronic Hemolytic Anemia (the Data for Four Years Are Representative of Periods of More than Ten Years for Each Patient).*

In the patient with Cooley's anemia the reticulocyte level was quite constant until the anemia was increased during pregnancy. Since the red-cell count was usually about 5 x 10^6/mm^3, with 5 per cent reticulocytes, the absolute count of reticulocytes was approximately 250 x 10^3/mm^3. The range in four years was 103 x 10^3 to 450 x 10^3/mm^3. The upper limit of normal of reticulocytes is about 90 x 10^3/mm^3.

The reticulocytes were variable in the patient with congenital hemolytic jaundice, who refused splenectomy. The red-cell count varied from 2.7 x 10^6 to 4.0 x 10^6 mm^3, and the absolute number of reticulocytes from 105 x 10^3 to 740 x 10^3/mm^3. The variability of the reticulocytosis is unexplained.

the preliminary evidence for blood destruction or blood loss (iron deficiency), the morphologic characteristics of the red cells and the changes in white blood cells and platelets. Correlation of these key data with the history and physical examination will usually permit the physician to classify polycythemia into one of the three classes in Table 1 and to place an anemia in one of the three major classes of anemia as indicated in Tables 3 and 4. For example, anemia of acute or subacute blood loss may be diagnosed from the data obtained by these examinations (see Table 3). The cause of blood loss is then sought. Special examinations that may be required for a specific diagnosis of certain anemias are outlined below.

In *polycythemia* the special tests are largely indicated from Table 1, but may include such examinations as needle aspiration or surgical biopsy of the bone marrow and biopsy of lymph nodes in suspected neoplastic disease. The blood volume may be studied since the increase occurs in the mass of red cells and not in the volume of plasma, which is normal.[120, 121] However, the hematocrit level is a good index of the mass of red cells.[117]

(3) Special Examinations for Hemolytic Anemias

The following special examinations may be indicated for detection of particular hemolytic anemias or mechanisms of increased destruction of red cells.

(a) Tests related to the red cells.

(i) Morphologic abnormalities of red cells as observed in Cooley's anemia, malaria (parasites), Oroya fever or Carrión's disease (intracellular *Bartonella bacilliformis*), lead poisoning (stippling), sickle-cell disease, thermal injury and poisoning from napthaline.[83]

(ii) Sickle-cell trait.*

(iii) Osmotic fragility of red cells.*

(iv) Mechanical fragility of red cells.*

(v) Osmotic and mechanical fragility of red cells observed on blood samples incubated for twenty-four hours at 37°C.*

(vi) Pigment changes such as methemoglobin and sulfhemoglobin.*

(vii) Bone-marrow aspiration or biopsy.

(b) Tests related to serum and red cells.

(i) Donath-Landsteiner test for cold autohemolysin*: positive in paroxysmal cold hemoglobinuria.

(ii) Hemolysis test with acidified serum*: positive in chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria.

(iii) Detection of incompatible red cells or plasma in transfusion: blood groups A, B, O and Rh.[68]

(iv) Detection of immune and hyperimmune anti-Rh antibodies: transfusion reactions and erythroblastosis fetalis.[68]

(v) Direct and indirect Coombs test, antiglobulin serum: erythroblastosis and acquired hemolytic jaundice.[68]

(vi) Detection of agglutinins effective at acid pH†; indirect Coombs test at acid pH: acquired hemolytic jaundice.

(vii) Hemolysins†; hemolysins effective at acid pH.

(viii) Detection of autohemagglutinins effective in the cold or at body temperature or both.†

(c) Agents related to increased destruction of red cells.

(i) Tests for quinine, sulfonamides or other chemicals in blood and urine.

(ii) Cultures for bacteremia.

(d) Tests related to pigments.

(i) Bilirubinemia.

(ii) Hemoglobinemia.†

(iii) Methemalbuminemia.†

(iv) Hemoglobinuria.†

(v) Hemosiderinuria.†

(vi) Fecal urobilinogen.

(vii) Urine urobilinogen.

(e) Biopsy of lymph nodes.

(f) Splenectomy is a form of therapy, the results of which may aid in diagnosis either as a biopsy or because of effects upon the formed elements of blood.

(g) Therapeutic trial with liver extract, vitamin B_{12}, folic acid or iron may be indicated.

(4) Special Examinations for Anemias due to Decreased Production of Red Cells

The following special examinations may be indicated for the diagnosis of certain of the anemias due to decreased production of red cells.

(a) Bone-marrow aspiration or biopsy.

(b) Therapeutic trial‡ with liver extract, vitamin B_{12}, folic acid or iron.

(c) Gastric analysis: achlorhydria and achylia in pernicious anemia; achlorhydria in idiopathic hypochromic anemia and certain other anemias.

(d) Liver function: anemia in chronic liver disease.

(e) Kidney function: glomerulonephritis; chronic uremia.

(f) Biopsy: lymph nodes (rarely of liver or spleen).

(g) Basal metabolism: myxedema.

(h) Examinations for infection: blood culture, sedimentation rate.

(i) Chronic lead poisoning: examination for stippled red cells and porphyrins.

(j) Therapeutic trial with irradiation or chemotherapy in leukemia and lymphoma.

6. History

(1) Polycythemia

(a) Relative polycythemia. Usually, in relative polycythemia, the history will provide clear evi-

*Discussed in detail in subsequent paragraphs.

†Discussed in detail in subsequent paragraphs.

‡The therapeutic response to liver and iron is described in the references[1-3, 7, 94, 98, 112] and is not discussed here (See Fig. 2 and 3).

dence for conditions associated with loss of plasma or dehydration (Table 1).

(*b*) *Arterial anoxia.* The outstanding symptoms of arterial anoxia are shortness of breath on exertion, and a history of blue color to the skin. There may also be the symptoms of the underlying illness such as heart disease or chronic disease of the lungs.

(*c*) *General symptoms of polycythemia.* An increase in hemoglobin and number of red cells may be asymptomatic or associated with headache, a feeling of fullness in the head, visual disturbances, dizziness, weakness and thrombosis.

(*2*) *Anemia*

(*a*) *General symptoms of decreased oxygen-carrying power of the blood.*

There is no one specific symptom that leads the clinician to suspect the diagnosis of anemia of moderate degree. In fact, chronic and moderately severe anemias represent some of the more occult conditions in medicine. The general symptoms of anemia include fatigue, lassitude, loss of vigor, loss of appetite, pallor, shortness of breath, tachycardia, pounding in the head and symptoms suggesting progressive heart failure. In acute blood loss, there may be the symptoms of syncope or shock.

(*b*) *Symptoms of increased destruction of blood.* These include jaundice, which may be clinically unrecognizable or manifest. The urine may be "dark" from an increase in pigments such as urobilin, occasionally bilirubin, hemoglobin and other pigments.

(*c*) *Other symptoms associated with anemia.* The chief symptoms of the patient with anemia may be related to the cause of the anemia, as in blood loss from external hemorrhage, hemoptysis, hematemesis, melena, menorrhagia and metrorrhagia. In pernicious anemia, however, there is the frequent association of symptoms of subacute combined system disease of the spinal cord, extreme loss of appetite, nausea or vomiting or symptoms of gall-bladder disease. In other cases there may be complications of the anemia. In chronic hemolytic anemia with increased excretion of blood pigments there may also be symptoms of gall-bladder disease.

The pathologic process causing anemia may cause other symptoms, exemplified as follows. In sickle-cell anemia, there may be symptoms of pain from thromboses in viscera or extremities. In leukemia, lymphoma and neoplastic disease, there may be the history of wasting, fever, enlarged spleen, lymph nodes, liver or other masses. Purpura and bruising may be a prominent complaint with anemia that is associated with thrombocytopenia.

(*d*) *History of exposure to toxic agents.* It is important to elicit the history of a patient's occupation, habits and ingestion of drugs to estimate possible exposure to chemical or physical agents causing anemia, such as x-rays, benzol (benzene), insecticides, moth balls, hair dyes, arsenic, lead, sulfonamides, gold therapy and fava bean.

(*e*) *Family history.* Occasionally the family history of anemia serves as the major clue to establishing a diagnosis of hereditary anemias such as congenital hemolytic jaundice, sickle-cell anemia, Cooley's anemia and Cooley's trait. Erythroblastosis fetalis is a congenital condition that is familial in incidence. In pernicious anemia, there may be a high family incidence of this disease.

7. Physical Examination

(*1*) *Polycythemia*

A red or cyanotic color of the lips, cheeks, hands, nail beds and feet is typical in polycythemia. The vessels of the scleras are frequently injected. Occasionally, there is little evidence of beefy color to the skin, and the diagnosis may not be made on physical examination. In arterial anoxia and methemoglobinemia there is marked cyanosis. There may or may not be splenomegaly, hepatomegaly, clubbing of the fingers and toes and, occasionally, signs of thromboses in extremities and other regions of the body.

(*2*) *Anemia*

(*a*) *Estimation of the hemoglobin level.* The presence of significant anemia is frequently missed by the physician because estimation of the hemoglobin level from the physical examination is notoriously unreliable, except in fairly severe anemias. An attempt should be made to estimate the hemoglobin level by examination of the color of the skin, nail beds and mucous membranes of the lips, the conjunctivas of the eyelid and the hypothenar eminences of the hands if they are warm.

(*b*) *Signs of increased blood destruction.* The only direct evidence of increased blood destruction may be the appearance of a trace of icterus seen only in the scleras when they are viewed in full daylight and easily missed in yellow artificial light. In general, it should be possible to estimate any significant increase of the icteric index by the color of the scleras near the iris and away from the subconjunctival fat, even though the yellow tint is slight. Occasionally, in prolonged hemolytic anemia, especially in chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria, the scleras appear bronze or a "muddy" yellow brown. The skin may show icterus in mild or moderate degree in conditions with increased blood destruction.

(*c*) *Physical changes associated with anemia.* Anemia per se may be associated with "hemic" murmurs and all the signs of heart failure.[116] In severe chronic anemia, prostration, syncope and delirium with or without fever may occur. In acute anemia varying degrees of weakness, prostration or shock with normal or subnormal temperature are observed. In pernicious anemia, there may be

the signs of subacute combined system disease of the spinal cord. In congenital hemolytic jaundice and Cooley's anemia, the spleen is frequently enlarged. In leukemia, lymphoma and neoplastic disease, there may be lymphadenopathy, hepatomegaly, splenomegaly or tumor masses. Purpura may be found with or without pallor of the skin concomitantly with anemia. The tongue may show varying degrees of atrophy and soreness. In patients with iron-deficiency anemia there may be spoon-shaped fingernails and difficulty in swallowing.[93]

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 36471

PRESENTATION OF CASE

First admission. A seventy-year-old woman entered the hospital because of vomiting of ten days' duration that began following the ingestion of lobster. Others eating the lobster had also become temporarily ill but had quickly recovered, whereas the patient continued to regurgitate practically all foods eaten and to have anorexia, nausea and vague upper abdominal distress. She had lost 12 pounds in weight since the onset of this episode.

She had been treated by her physician for two years for high blood pressure and anginal attacks with digitalis and nitroglycerine. These attacks consisted of episodic pressing chest pain radiating to the left mid-forearm, following exertion, heavy meals or excitement. She had avoided fatty foods because they tended to produce indigestion. She had lost 40 pounds in weight over a three-year period but had been on a reducing diet.

Her appetite had always been hearty. She had always preferred cold weather, had been intolerant of heat, had perspired easily, had been overactive and had been easily disturbed emotionally. The past history otherwise revealed excellent general health, and the present hospital admission was her first. The menopause had occurred thirty years before, and there had been no subsequent spotting or discharge.

Physical examination revealed a well developed, obese, overactive, pink-faced woman in no acute distress. There was a slight staring expression of the eyes but no exophthalmos or lid-lag. The brow was slightly moist, and the skin warm. The thyroid was difficult to outline accurately but was soft and felt to be diffusely enlarged to two or three times the normal size. There was no bruit or thrill. The chest was clear. The blood pressure was 160 systolic, 80 diastolic. The pulse was 96 and regular. The heart border was 10 cm. from the midsternal line, with a short Grade II apical systolic murmur. The liver edge was 4 cm. below the costal margin and was slightly tender. The upper border was percussed at the level of the sixth rib. Pelvic examination was negative.

The urine was cloudy amber, had a specific gravity of 1.022 and gave negative tests for albumin and sugar. The sediment contained 8 to 10 white cells per high-power field. Examination of the blood revealed a red-cell count of 4,250,000, with a hemoglobin of 12.5 gm., and a white-cell count of 8250, with 73 per cent neutrophils, 23 per cent lymphocytes and 4 per cent eosinophils. A stool was brown and guaiac negative. The nonprotein nitrogen was 27 mg., the fasting blood sugar 108 mg., the total protein 7.2 gm., the albumin 3.9 gm. and the globulin 3.3 gm. per 100 cc. The cephalin flocculation was + in forty-eight hours, the bilirubin normal and the prothrombin time 19 seconds (normal, 17 seconds). The bromsulfalein test showed 6 per cent retention of the dye in forty-five minutes. The protein-bound iodine was 10.6 gamma per 100 cc. Electrocardiograms were normal except for flat T waves. Five basal metabolic rates ranged from +34 to +40 per cent. A blood Hinton test was negative. She excreted 39 per cent of a tracer dose of radioactive iodine in forty-eight hours.

X-ray studies showed an 8-cm. soft-tissue density almost at the midline of the upper chest anteriorly that displaced the trachea somewhat to the right. The right-lung field was clear. The aorta was tortuous and calcified in the arch. There was a soft-tissue density about 4 cm. in diameter in the region of the apex of the heart and the left costophrenic angle. A barium-enema examination revealed multiple diverticula in the sigmoid and descending colon and a solitary one in the ascending colon. There was slight mucosal thickening in the region of the diverticula in the proximal sigmoid, but the large bowel was otherwise normal. Multiple faceted gallstones were seen in the gall bladder. The sigmoid was displaced slightly upward by a soft-tissue mass in the pelvis.

The patient's vomiting quickly subsided on a soft diet, and she was comfortable except for approximately daily episodes of angina quickly relieved by nitroglycerine. She was given 12 millicuries of radioactive iodine and was discharged, to be followed in the Out Patient Department. Forty and five-tenths per cent of this was excreted in forty-eight hours.

Final admission (two and a half years later). Following discharge she improved rapidly, and within a two-month period she was able to return to full housekeeping, no longer fearing the angina. The attacks lessened in frequency to one

every one or two weeks, and she reported that she had obtained a new lease on life. The protein-bound iodine, when checked three months after discharge, was 6.8 gamma per 100 cc., and eight months after discharge she was found to excrete 69 per cent of a tracer dose of radioactive iodine. Despite this, the basal metabolic rates remained elevated, varying from +12 to +34 per cent. The blood pressure was approximately 200 systolic, 100 diastolic, on numerous occasions. The improvement was well sustained until approximately five months prior to this admission, when she began to note increasing frequency of anginal attacks, increased appetite and a weight loss of 8 pounds. A tracer dose of radioactive iodine a month before entry showed an excretion of 67.7 per cent and a protein-bound iodine of 8.98 gamma per 100 cc. Two days before admission the anginal attacks became very severe, with pain radiating across the precordium, down both arms and into the back. Nitroglycerine failed to bring complete relief. The pain then became almost constant, requiring hourly nitroglycerine with little relief. She vomited small amounts of food several times. She was weak and sweaty but not dyspneic. There had been no other symptomatic changes.

Physical examination revealed an obese, pale woman complaining of substernal and epigastric pain radiating across the left lower anterior chest. She was not dyspneic but preferred to sit upright in bed. The skin was cold and moist. The neck veins were flat. The thyroid could not be definitely outlined, but there was a questionable mass on the left. The blood pressure was 168 systolic, 100 diastolic. The pulse was regular at 100. There was otherwise no change from the previous examination of the heart or abdomen. The liver edge was still palpable 2 or 3 cm. below the costal margin. The lungs were clear.

The urine had a specific gravity of 1.022 and contained a trace of albumin, with 1 to 2 white cells per high-power field in the sediment. The white-cell count was 11,800, with 87 per cent neutrophils. The hemoglobin was 16 gm.

Her condition rapidly deteriorated, and three hours after entry she was in marked respiratory distress, ashen and cyanotic, with bubbling rales in the chest. The blood pressure was 140 systolic, 110 diastolic. The heart rate was 40 and regular. The extremities were cold, with weak pulses. She responded fairly well to oxygen, morphine and tourniquets and the rales cleared somewhat. However, she died quietly twelve hours after admission.

Differential Diagnosis

Dr. A. Stone Freedberg*: Did this patient have any fever?

Dr. Tracy B. Mallory: No.

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Dr. Freedberg: Following the tracer doses of radioactive iodine, were direct Geiger–Mueller counts made over the thyroid gland or the chest or pelvic masses?

Dr. Earle M. Chapman: I believe the first tracer dose was given to study the urinary excretion. At that time direct counting over the thyroid gland was not done here. I believe we did screen the pelvic mass after the second dose of radioactive iodine.

Dr. Freedberg: I should like to ask what symptoms improved after the radioactive iodine was given — the increased appetite, overactivity, intolerance of heat or the angina pectoris?

Dr. Chapman: All symptoms improved, and the anginal attacks lessened in number and frequency.

Dr. Freedberg: Since this history is so lengthy and so full of confusing findings, it might be preferable to discuss the terminal illness first. The exacerbation of angina pectoris followed by status anginosus, the severe prolonged pain not relieved by nitroglycerine, the peripheral vascular collapse and the pulmonary edema were all consistent with the diagnosis of acute myocardial infarction. The slow heart rate is of some interest. Slow heart rates are commonly seen in acute posterior-wall myocardial infarctions. Were electrocardiograms made during the terminal illness? If they were, I would guess they showed changes consistent with this diagnosis.

Dr. Mallory: The patient had only a cardiette examination and that note reads, "since the previous tracing there has been considerable increase in ST and T wave abnormalities consistent with coronary insufficiency with subendocardial necrosis. No QRS evidence of transverse infarction." That is the only note.

Dr. Freedberg: One can only guess whether an acute coronary occlusion was present. Approximately 40 per cent of acute myocardial infarcts in hearts studied by the Schlesinger technic show no acute coronary occlusion. There were two circumstances in this case, however, that might have been associated with the deposition of ante-mortem clots. These are the repeated administration of nitroglycerine with consequent hypotension and the presence of peripheral vascular collapse. As you may know, Blumgart, Schlesinger and Zoll[1] reported on 8 patients who died with peripheral vascular collapse due to various conditions in whom multiple fresh coronary occlusions were found at post-mortem examination.

It is reasonable to assume that this patient had coronary-artery disease. The presence of thyrotoxicosis in a patient with high blood pressure is, of course, adequate for the development of angina pectoris. It is of some interest, however, that of 177 patients with angina pectoris studied by the Schlesinger technic only 10 per cent had angina pectoris in the absence of coronary-artery disease. These patients had valvular heart disease, valvular

heart disease with hypertension or hypertension alone.[2]

One should mention in passing other possibilities that might account for the terminal clinical picture, such as dissecting aneurysm, pulmonary embolism, acute pericarditis and acute myocarditis, but I find little to support these in the history.

The problems in this patient, I believe, were whether or not the patient had thyrotoxicosis. Was the terminal event ushered in by recurrent thyrotoxicosis? What was the nature of the various masses that she had? What was the relation of these masses to the clinical picture? Perhaps this would be a good time to see the x-ray films.

DR. STANLEY M. WYMAN: The chest films show a rather large mass lying to the left of and anterior to the trachea at about the level of the clavicles. This compresses the trachea from in front.

DR. FREEDBERG: Is there any calcification in it?

DR. WYMAN: Not that I can be sure of. It is in a difficult place to rule out calcium.

DR. FREEDBERG: Was the patient fluoroscoped? Did the neck mass pulsate or show any movement on swallowing?

DR. WYMAN: The patient was fluoroscoped, but no mention was made that the mass moved on swallowing or pulsated.

DR. FREEDBERG: Could the mass at the apex of the heart represent pericardial fat?

DR. WYMAN: It lies quite far forward apparently against the chest wall and diaphragm anteriorly. I would like to know whether that was so by fluoroscopy. It certainly could represent pericardial fat.

DR. FREEDBERG: It could not possibly be a diaphragmatic hernia?

DR. WYMAN: I do not believe so. I think the diaphragm can be well traced, and I think the shadow lies in the chest itself and does not represent a hernia. I am not sure what its nature is, but I am not impressed by it.

The barium-enema examination shows a soft-tissue mass in the left bony pelvis that seems to displace the rectosigmoid slightly toward the right. It was probably more apparent to the fluoroscopist than it is on the film. There is some spasm in the region of the diverticula.

DR. FREEDBERG: The mass was not palpated by the fluoroscopist?

DR. WYMAN: No; there is no note of that. The gallstones are clearly evident.

DR. FREEDBERG: Was any change noted in these masses by x-ray examination subsequent to the administration of radioactive iodine?

DR. WYMAN: I do not believe she had any subsequent films.

DR. FREEDBERG: I find myself in the very unenviable but I suppose not unusual position of not being able to give a positive answer to the various questions that I have raised.

The diagnosis of thyrotoxicosis was warranted in this patient although some of the usual features were absent and some of the features present were unusual. There was a history of heat intolerance, some increased appetite, easy perspiration, labile emotional state, overactivity and weight loss. All of these, however, may be found in obese people in the absence of hypermetabolism. Thyrotoxicosis has been observed to occur following a period of weight reduction. Moreover, tremor, palpitation and fatigue — common symptoms in thyrotoxicosis — are not mentioned. About half the patients with thyrotoxicosis and heart disease show congestive failure or cardiac arrhythmias; this patient had neither. Relief of angina pectoris following I^{131} therapy has been observed in patients with thyrotoxicosis following an interval of six to twelve weeks, when the metabolism falls to a euthyroid level. We have also observed relief of angina pectoris in euthyroid persons given large doses of I^{131} in about six weeks at the earliest; at this time evidence is present of hypometabolism, and the serum cholesterol is elevated.[3]

The physical findings were in some respects consistent with the diagnosis of thyrotoxicosis. The patient did have a rapid pulse rate, a rather wide pulse pressure, some stariness to the eyes and a palpable mass in the neck that was demonstrable on the x-ray films and that one would like to believe was a goiter. All these findings add considerable weight to the diagnosis of thyrotoxicosis. There was, however, no thyroid bruit or thrill. Auricular fibrillation was not present, and since no report was made of heart sounds, I should imagine they were not impressively overactive.

The laboratory data, again, were equivocal except for the elevated serum protein-bound iodine. This was in the range observed in patients with thyrotoxicosis. The basal metabolic rates were consistently elevated but were in the range observed in some patients with hypertension. Elevation of the basal metabolic rate in patients with hypertension, however, has, in my experience, occurred with rather marked, persistent hypertension.

The I^{131} tracer studies are difficult to interpret, but they fit best, in my opinion, with a diagnosis of toxic nodular goiter. The types of I^{131} studies that are being done in various clinics, including ours, are roughly three. One type is to measure the I^{131} uptake in the thyroid gland directly following a tracer dose by means of a system of Geiger-Mueller counters[4] or by a single tube. This gives us direct evidence of the avidity of the gland for the isotope. In some clinics, the urinary excretion of I^{131} is measured; then the difference between this urine excretion and 100 per cent is assumed to be the amount in the thyroid gland. Actually, that is not so. In many euthyroid subjects in whom we have measured the thyroid uptake and urinary excretion, one does not account for approximately

20 per cent of the dose at the end of twenty-four hours. In patients with thyrotoxicosis one does not account for approximately 10 per cent of the dose at the end of twenty-four hours. In this patient the urinary excretion was 40 per cent. On that basis, I would estimate that the uptake was 50 per cent in the thyroid gland, and assume that 10 per cent was distributed elsewhere. Since the urinary excretion measured was minimal — assuming that all the urine was collected and contained 40 per cent — the most that this patient could have had in the thyroid gland was 50 per cent. This is low for thyrotoxicosis. In patients with thyrotoxicosis and a diffusely enlarged thyroid the I^{131} thyroid gland uptake averages 70 per cent[5] with a standard error of 1.5 per cent. However, a small group of thyrotoxic patients with nodular goiter reported by Werner et al.[6] had smaller uptakes. We also have had a small group of patients with nodular goiter and thyrotoxicosis in whom the uptakes were within the range of 60 per cent rather than in the range of 70 per cent.

Another test that may give additional information on whether one is dealing with hyperthyroidism is to measure the rate of elimination of the isotope from the thyroid gland — for example, the rate at which the thyroid gland turns over the material. This has been termed the biologic half life and is defined as the number of days for the amount of I^{131} present in the thyroid gland to decrease by 50 per cent. The measurement thus includes elimination from the gland and physical decay. The biologic half life in euthyroid persons is approximately seven days (standard error 0.4 days).[5] Patients with thyrotoxicosis have a biologic half life of five and six-tenths days with a standard error of two-tenths day. Patients who have been treated with I^{131}, and this is pertinent to the case under discussion, demonstrate an even faster turnover. Thus, a thyrotoxic patient treated with I^{131} can become euthyroid both clinically and by the various laboratory procedures, such as the basal metabolic rate and protein-bound iodine. We find in these patients that following an I^{131} tracer the biologic half-life rate is even faster than when the patient was hyperthyroid.

The third type of study is the determination of the rate or amount of conversion of the isotope to a protein-bound form. Some preliminary studies that have been made by several groups, by Clark[7] in Chicago and by Freedberg et al.,[8] have shown that patients with thyrotoxicosis will have a larger quantity of protein-bound I^{131} in the serum twenty-four hours after a tracer dose than normal persons. Furthermore, the ratio of serum protein-bound I^{131} to inorganic I^{131} is greater in thyrotoxic patients. In a small group of hyperthyroid subjects we found an average of 68 x 10^{-5} microcuries per cubic centimeter for each 150 microcuries administered whereas euthyroid subjects average 13 x 10^{-5} microcuries for each 150 microcuries administered.[8]

The multiplicity of studies all illustrate the difficulty of diagnosis in borderline thyrotoxicosis or in atypical cases.

I might say a word about the dose that was given. I have made some very rough calculations assuming that the biologic half life was about six days and that the thyroid gland weighed 80 gm. and took up 50 per cent of the dose in twenty-four hours. The radiation dose apparently was about 10,000 equivalent r, which is approximately the dose that has been used in our thyrotoxic patients at the Beth Israel Hospital. Given in a single-dose, this has resulted in an euthyroid state of the patient in about 50 per cent and hypothyroidism in approximately 15 per cent of our series.

One should briefly consider other causes of hypermetabolism. It is not uncommon to find hypermetabolism in patients with heart disease and particularly in patients with hypertension. However, the tracer studies that we have done and that have been done elsewhere have not shown any increased avidity of the thyroid for radioactive iodine, nor is there, to my knowledge, any elevation of the serum protein-bound iodine in nonthyrogenous cardiac disease or in hypertension. Other causes of increased metabolism, such as lymphoma, leukemia and pheochromocytoma, are not very tenable explanations for this patient's clinical course.

One should consider the possibility of other thyroid tumors, particularly thyroid carcinoma. There is no evidence that will permit one to make a diagnosis of thyroid carcinoma in this patient. The neck mass was soft, and there was no lymphadenopathy. I do not believe the chest lesion was a metastasis although one cannot completely exclude it. Patients with thyroid carcinoma, in our experience, do not commonly have an increased uptake in the thyroid tumor, although a small number, approximately 15 per cent, demonstrate an avidity.

I think that is as far as I can go. The diagnosis I shall make is toxic nodular goiter, with angina pectoris and status anginosus, coronary-artery disease, acute myocardial infarction and ? acute coronary thrombosis.

Dr. Chapman: I have enjoyed hearing about Dr. Freedberg's experience in treating patients with thyrotoxicosis. I might say that our experiences were similar with a single exception. We have not found that the distribution of the radioactive iodine is as variable in such a high percentage as he gave. In our experience the percentage in urine excretion and in thyroid uptake together prove much closer to the total dose than the figures given, although we sometimes have a difference of 5 to 10 per cent. Thus, when the patient re-entered the hospital for another tracer dose a month before death, there was a urinary excretion of 67 per cent,

and the thyroid uptake measured 37 per cent, making a total of 104 per cent.

Dr. Freedberg: That is exactly what I illustrated. If the turnover following I^{131} therapy was more rapid, in twenty-four hours she would have had an even higher percentage of thyroid uptake than 37, perhaps in the range of 40 or 45, so that, of course, would be in the lower range of thyrotoxicosis, or toxic nodular goiter.

Dr. Chapman: That was the problem. This woman had persistent and continued angina pectoris. The last note I wrote was as follows: "The question is whether after having a normal protein bound iodine and tracer after treatment and response, she has now truly relapsed." That was the point that we were trying to determine before the final episode. I would like to ask Dr. Maloof if he would say something about the therapy.

Dr. Farahe Maloof: In Graves's disease, we have found an excretion of 37 per cent of I^{131} in forty-eight hours to be compatible with the lower range of toxicity. In patients with toxic nodular goiter, we have found the uptake of radioactive iodine to lie in a lower range than in patients with Graves's disease. Following the therapeutic dose, she excreted 67 per cent of the I^{131} in forty-eight hours, which is normal, and had a normal protein-bound iodine, and we thought that she was euthyroid in spite of the basal metabolic rate. Lately, she was again experiencing cardiac difficulties, and a repeat tracer dose of I^{131} was normal, but the protein-bound iodine (8.98 gamma per 100 cc.), was borderline or slightly high — however, it represented a change from the previous protein-bound iodine of 6.88 gamma per 100 cc. Since the protein-bound iodine of 8.98 gamma per 100 cc. merely represents one determination, the answer has to be equivocal, but it is my impression that she may have had a mild recurrence of toxicity in spite of the normal uptake of radioactive iodine. It is unfortunate that she died so suddenly. We should have given her a large dose of radioactive iodine just before her death so that an autoradiograph might have been obtained and might have had some value in determining thyroid function. We know that histology does not always correlate exactly with function and that the uptake of radioactive iodine, the basal metabolic rate and the protein-bound iodine all represent different functions of the thyroid. From animal work started by Dr. Bengt Skanse and being continued at present, the various biologic activities of the thyroid gland — namely, the uptake of radioactive iodine, the ability to respond to the antithyroids and to thyroid-stimulating hormone — differ in their response to radiation with I^{131}. We have seen patients with Graves's disease who are still clinically toxic six months after a therapeutic dose of radioactive iodine, whose basal metabolic rates are high, whose protein-bound iodine determinations are high and whose uptake of radioactive iodine is in our "normal range." This "range" needs to be defined in irradiated glands. I am not quite clear on Dr. Freedberg's statement that a gland that has been irradiated should have a more rapid turnover — although the time factor may be important here. This is a very interesting observation.

Dr. Freedberg: It has been our experience that the turnover is faster.

Dr. Samuel McD. McCann: I wonder if after the radiation, since a large proportion of the cells are knocked out, the remaining cells are metabolizing faster and therefore the turnover is faster.

Dr. Freedberg: That is one of the working hypotheses, but we have no definite proof for it.

Clinical Diagnoses

Myocardial infarction.
Hypertensive and arteriosclerotic heart disease.
Hyperthyroidism, with substernal goiter.

Dr. Freedberg's Diagnoses

Toxic nodular goiter.
Angina pectoris, status anginosus.
Coronary-artery disease.
? Acute coronary thrombosis.
Acute myocardial infarction.

Anatomical Diagnoses

(*Thyrotoxicosis and angina pectoris treated with radioactive iodine.*)
Nodular goiter, with involution.
Coronary occlusion, with old and recent myocardial infarction.

Pathological Discussion

Dr. Mallory: I do not know that we can answer many of the problems that have been raised. The patient had a very large nodular goiter that seemed to lie almost entirely in the neck and to extend to a very slight degree into the upper mediastinum. Grossly, the gland looked like a large nodular colloid goiter that no one would suspect of hyperactivity. Microscopical sections showed that the acini were separated, involuted, very large and filled with colloid. The epithelial lining and the acini were low and flat — again no histologic suggestion of hyperactivity. There were foci of fibrosis in the gland that may have been due to radiation although they may be seen in any large colloid goiter. We found no evidence of a mediastinal mass. The mass in the pelvis was a fibroid attached to the uterus. There were gallstones and diverticula in the sigmoid.

The heart showed very severe coronary-artery disease. There was only slight hypertrophy; it weighed 380 gm. All coronary branches were calcified. The right was fairly widely patent but had paper-thin walls. The descending branch of the left demonstrated old occlusions and one area that was interpreted at the time of autopsy as possibly a fresh occlusion but on microscopical section appeared to be hemorrhage into an old atheromatous plaque.

The left circumflex branch showed extensive occlusions that were all entirely old. The myocardium disclosed a combination of old fibrous scars, particularly in the interventricular septum, and quite fresh myocardial infarction, which was irregularly and patchily distributed.

DR. JAMES H. CURRENS: Was there pericardial fat?

DR. MALLORY: There is always some fat there so that we do not necessarily pay much attention to it. The patient was a rather obese person.

A PHYSICIAN: What did the lungs show?

DR. MALLORY: The lungs showed only a moderate grade of pulmonary edema and were otherwise normal.

DR. CHAPMAN: The response of this patient to the therapy was quite dramatic, and she went home and led a very vigorous life. I would have expected the thyroid gland to be smaller than it was. Could you tell us the weight of the gland?

DR. MALLORY: It was 145 gm.

DR. CHAPMAN: The actual weight was far over our estimation of 30 or 40 gm.

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CASE 36472

PRESENTATION OF CASE

A thirty-three-year-old man was admitted to the hospital because of a left-upper-quadrant mass.

He had had occasional, minimal, vague costovertebral-angle pain and tenderness for two or three years that came on when he stood or rode for long periods. The pain seemed to radiate along the costal margin to the anterior axillary line but not to the groin. There was no recent increase in frequency or severity of the pain. Three weeks prior to entry while lying in bed he had palpated a mass in the left upper quadrant that he thought had become somewhat larger and firmer in the interval preceding admission. There was no pain or other symptoms associated with the mass.

He had always been in good health except for long-standing, nebulous gastrointestinal complaints, which he described as a "tight, tense stomach" and "an uncomfortable feeling" in the upper abdomen. He had consumed large quantities of beer during most of his adult life (about 6 quarts on week ends) but had discontinued this about six months before admission because of the symptoms described above and because he feared it might lead to serious illness. He had lost 8 to 10 pounds during this period of abstinence.

He had not been allowed to play basketball in school and had been rejected for military service in 1942 because of a cardiac murmur, which, he had been told, indicated rheumatic heart disease. He had had no symptoms referable to the heart, however, and had never limited his activities. There was no history suggestive of rheumatic fever, nor could he recall any of the usual childhood diseases.

On physical examination there were no palpable superficial lymph nodes. The heart was not enlarged, but there was a high-pitched Grade II systolic murmur, loudest at the third interspace just to the left of the sternum. A low-pitched, late diastolic murmur was heard in the same location by one observer but was not confirmed by others. Examination of the abdomen revealed a large, firm, left-upper-quadrant mass extending from beneath the costal margin downward half the distance to the umbilicus, medially close to the midline and laterally to the posterior axillary line. It was somewhat bound down on its lateral border but was otherwise movable. The mass could be separated from the liver, which was not enlarged, but could not be separated from the spleen. It was notched inferiorly and also on its right border near the costal margin. A transmitted pulsation was felt. The only other finding was a left varicocele.

The temperature, pulse and respirations were normal. The blood pressure was 110 systolic, 70 diastolic.

Repeated urine studies revealed specific gravities ranging from 1.005 to 1.030, ++ to +++ tests for albumin, no sugar and occasional red and white cells in the sediments. Examination of the blood disclosed a red-cell count of 4,100,000, with 15 gm. of hemoglobin, and a white-cell count of 9800,with 70 per cent neutrophils, 24 per cent lymphocytes, 4 per cent monocytes, 2 per cent eosinophils and adequate platelets. The sedimentation rate was 1.0 mm. per minute. The nonprotein nitrogen was 22 mg., the cholesterol 217 mg., the total protein 7.7 gm., the albumin 5.58 gm., the globulin 2.12 gm., the phosphorus 2.6 mg., the alkaline phosphatase 3.2 units and the calcium 9.9 mg. per 100 cc. The prothrombin time was 18 seconds (normal, 20 seconds), the bleeding time 4.5 minutes, the clotting time 4.5 minutes and the clot retraction normal.

The tourniquet test was negative. Bone-marrow studies showed no abnormalities. Roentgenographic studies, including a barium-enema examination, a gastrointestinal series (Fig. 1) and intravenous and retrograde pyelograms, revealed a large mass in the left upper quadrant with poorly defined margins. The mass displaced the stomach to the right and anteriorly and depressed the splenic flexure of the colon. It appeared to lie anterior to the lower pole of the kidney. The urinary passages appeared intrinsically normal. The upper portion of the ureter appeared to lie slightly more laterally than usual, and the lower portion over the sacrum lay quite far medially. On some films it was thought that the tip of the spleen could be outlined separate from the mass. A chest film revealed a well defined mass in the left hilus thought to represent enlarged lymph nodes.

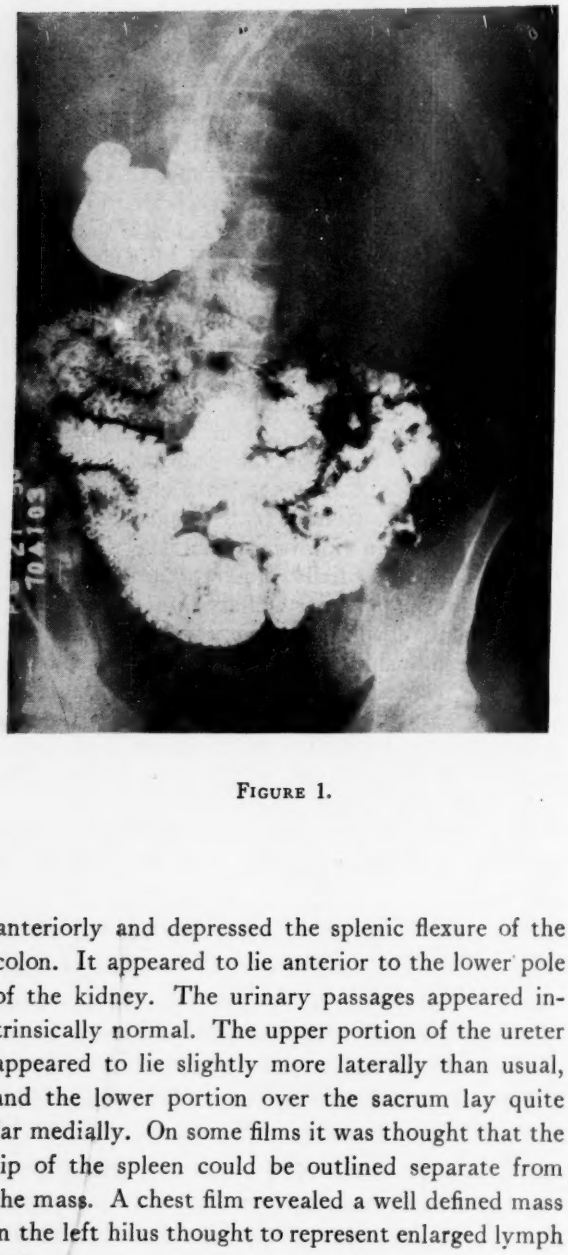

FIGURE 1.

The patient's general condition remained unchanged during the hospital stay, and there was no discernible change in the mass. However, a left axillary lymph node became palpable and was removed under local anesthesia on the fifteenth hospital day. It was reported by the pathologist to be a hyperplastic lymph node with no evidence of specific disease.

On the twenty-first hospital day a laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR. CHARLES B. BURBANK*: A thirty-three-year-old man, who had been perfectly well most of his life, had a story of two or three years of vague pain in the left flank, "nebulous" gastrointestinal complaints and an uncomfortable feeling in the stomach. However, he had apparently never limited his activities. I cannot see very much in this history that is helpful in the diagnosis. I shall have to depend on the physical examination and laboratory data for the diagnosis of the large left-upper-quadrant tumor. I may say that other than the x-ray films these are not helpful.

The protocol described a large, firm tumor extending from the costal margin halfway down to the umbilicus, over to the midline and laterally to the posterior axillary line. It was said to be fixed laterally but to be otherwise movable. I do not know quite how to interpret that. If a mass is fixed, it should not be movable.

Do you have the x-ray films?

DR. STANLEY M. WYMAN: The chest films show a large, rounded shadow at the upper pole of the left hilus. This is superimposed on the region of the main pulmonary artery and the left-main-pulmonary-artery branch. I think, in addition to the possibility that this represents lymph nodes or tumor in this region, one should include the possibility of enlargement of the main pulmonary artery itself, either idiopathic or associated with pulmonic stenosis. The lung fields appear clear, and the heart shadow is not grossly remarkable. A large, ill defined mass can be seen on all films of the abdomen (Fig. 1). On one film the tip of the spleen can be separated from the mass. The kidney seems to be displaced outward, and the ureter in its lower portion is displaced medially. In the oblique view the mass can be seen extending down below the kidney and anterior to it.

*Assistant in surgery, Massachusetts General Hospital.

DR. BURBANK: The mass does not seem to be attached to the stomach; the stomach is merely displaced?

DR. WYMAN: The mass is not attached to the stomach. It pushes the stomach to the right toward the midline so that presumably the mass could well be retroperitoneal.

DR. BURBANK: In discussing tumors of the left upper quadrant, one thinks first of all of splenomegaly of one sort or another. Certainly, I cannot say definitely that was not present here although there was a suggestion of a normal-sized spleen separate from the mass. Splenomegaly can occur with Banti's disease and Gaucher's disease and occasionally with tumor. Both the former diseases usually cause an anemia and have a prolonged history. Of course this man may have had the mass for two years, accounting for the slight pain. Amyloid disease would produce a large spleen, but there was nothing to suggest it; the patient had been too well all his life. Other splenomegalies, I think, can be ruled out by the negative history and normal blood studies.

When I read this history the first time I thought, since he had been a beer drinker, that perhaps he had cirrhosis and an enlarged left lobe of the liver, but that is ruled out by abdominal palpation and the x-ray findings.

A lesion of the tail of the pancreas might explain the mass, but tumors of the pancreas of this size are practically unknown. A cyst of the tail of the pancreas is a possibility. Usually, cysts of the pancreas are preceded by trauma or by repeated bouts of pancreatitis. There are a few congenital ones, to be sure, but they are rare. As far as I know the mass was of recent origin. Kidney tumors — a polycystic kidney — should be considered. The normal pyelograms, both intravenous and retrograde, give good evidence that the mass was not in the kidney. Also, in one lateral film the mass was seen to be somewhat anterior to the kidney.

I had thought it might have been a pedunculated sarcoma arising from the stomach and extending into the left upper quadrant, but there was no evidence of that in the x-ray films. In that event one would expect the stomach to be pulled over toward the mass, but it does not seem to have been.

When the patient first entered the hospital there were no palpable lymph nodes. On the fifteenth hospital day a lymph node was palpable and was biopsied. There was also something in the left hilus. Of course, one would like to find one explanation for the axillary lymph node and the hilar and abdominal masses. One thinks of the retroperitoneal tumors that could do this. If this was a reticulum-cell sarcoma or lymphosarcoma, lymph nodes in the chest and in other places in the body could perfectly well have occurred. My opinion is that this was not a lesion of the spleen, kidney or pancreas but a retroperitoneal tumor, and I would guess it may well have been a lymphosarcoma, with involvement of the lymph nodes in the chest and perhaps elsewhere. The fact that the ureter was pushed away slightly, I think, is in favor of a retroperitoneal location.

A PHYSICIAN: I wonder if the albuminuria and cells would throw any light on the situation?

DR. BURBANK: I was inclined not to attach too much importance to that. I thought the pressure alone could perhaps account for the cells. I do not think I can explain the albuminuria.

CLINICAL DIAGNOSIS

Primary splenic tumor, ? splenic cyst.

DR. BURBANK'S DIAGNOSIS

Retroperitoneal lymphosarcoma.

ANATOMICAL DIAGNOSIS

Leiomyosarcoma, retroperitoneal, with invasion of tail of pancreas, hilus of spleen and splenic vein.

PATHOLOGICAL DISCUSSION

DR. GEORGE L. NARDI: I am afraid that Dr. Burbank was much more astute than we were. We saw this patient in consultation and ruled out generalized systemic disease and transferred him to the Surgical Service with a diagnosis of splenomegaly. The preoperative diagnosis was primary splenic tumor, probably splenic cyst. Because of its large size, a thoracoabdominal incision was made, and I was surprised to find a small spleen at the point where Dr. Wyman pointed it out astride a huge mass filling the lesser omental sac. This was freed without much difficulty and was removed. In its removal we had to take a small piece of the tail of the pancreas. The report on the frozen section at operation was sarcoma invading the tail of the

pancreas going down to the superior mesenteric vessels. It was found that there was invasion of the parenchyma of the pancreas and the splenic vein at this site, and since the operation had not taken too long, we went ahead and did a total pancreatectomy.

Dr. David Freiman: As Dr. Nardi has indicated, the mass was large, multinodular and retroperitoneal, measuring about 20 cm. in diameter. A layer of shining peritoneum covered its anterior surface. The largest portion of the mass lay in the region of the hilus of the spleen and tail of the pancreas, both of which were invaded by tumor (Fig. 2 and 3). The rest of the spleen was small and distant from the mass. On section the tumor tissue had a whorled appearance. It had invaded the main portion of the splenic vein above the tail of the pancreas and had extended into four major branches within the spleen that were obstructed by tumor. That portion of the head of the pancreas and body of the pancreas which was removed in the subsequent procedure, as well as the lower portion of the stomach, the duodenum and the upper portion of the jejunum, showed no evidence of tumor invasion. On microscopical section the tumor proved to be a sarcoma composed of spindle cells having the appearance of smooth muscle. Multinucleated tumor giant cells were numerous. Special stains showed definite myofibrils. I think there can be no doubt that this was a leiomyosarcoma arising in the retroperitoneal tissues or possibly in the tail of the pancreas.

Figure 2.

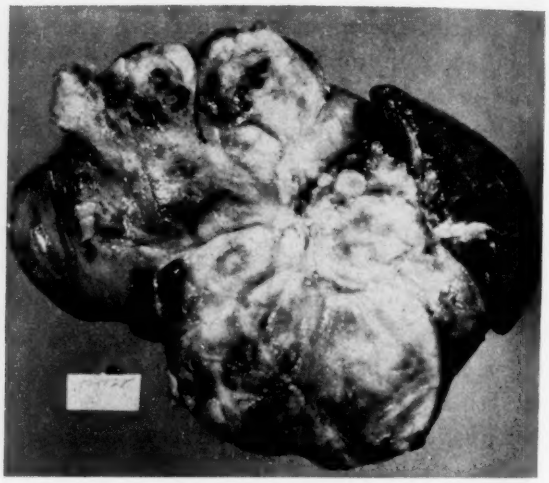

Figure 3.

Dr. Jacob Lerman: Has the mass in the chest changed?

Dr. Nardi: The mass in the chest has not shown much change so far. The patient has done remarkably well. The diabetes has been controlled on 20 to 30 units of insulin on a full diet.

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COLD TURKEY

Today is Thanksgiving, so far as the date of this issue of the *Journal* is concerned, regardless of the day when it may appear upon the desks of its readers, or be opened by them. The feast has been established and proclaimed according to tradition, and, as the biter is sometimes bit, so the gobbler is being gobbled.

As the aftermath of Thanksgiving is cold turkey, however, a reflection on the way in which man has used those resources for which he should be thankful may be cold comfort.

There is general evidence today that much of mankind has lost any secure ethical or moral moorings and is adrift upon a rising sea of troubles. Whole populations are suffering more dreadfully than they have been made to suffer for generations, and countless persons, even in a country as apparently secure as this has been until now, are wandering with neither spiritual nor intellectual guidance, and with no inner resources.

Not only are corruption and evil accepted as almost never before, with a disturbing complacency, but crimes of passion and acts of violence that result from emotional instability are of daily occurrence. The earth's most troublesome biped, having forsaken true values and having accepted material goals and rewards, now imagines himself to be forsaken when he finds that his achievements do not bring satisfaction.

At the risk of seeming to make an excursion, perhaps unwarranted, into the precincts of morality or even religion, one might ask what the true values are that appear to be so neglected and that might turn man's chronic discontent into something a little more divine.

A number of changes in outlook could be mentioned that would help to put some starch into his character and give the individual a strengthening objectivity. There might be a renunciation of his share of the mass selfishness that is so prevalent in the world. There might be a determination that there shall be no appeasement of evil, no compromise with corruption and no placid acceptance of mediocrity.

A consciousness of the forgotten man and a clearer concept of one's duty to him instead of indifference or mere vociferation in his behalf must be developed. This must come also from the heart, since a worthy emotion may take precedence over an intellectual achievement, for as Thomas à Kempis said, it is better to feel pity than to be able to define it. Accompanying this awareness of their plight there must be a strong resolve to secure for the oppressed millions of the world, on every continent, those freedoms with the promise of which countless human beings are now being deluded by the opponents of ethics and morality. There must be a determination to seek the truth candidly and to accept it with humility.

If enough of such strength can be added to the fibers of enough persons, then the nation will have gained something for which it can be truly thankful!

HOSPITALIZATION OF THE MENTALLY ILL

It is one of the commendable and happy episodes in the record of man's activities that Philippe Pinel, in 1793, instituted reforms in the treatment of the mentally ill. In the face of prejudice and ignorance he succeeded in having chains and manacles removed from the insane patients — actually prisoners — in the Bicêtre hospital. The world has long since applauded him.

However, in man's dealing with man there is at least suggestive evidence that any presumable course toward betterment could not be represented by a consistently upward curve or line. If Pinel believed in progress and if today he could scan some aspects of the treatment of the mentally deranged he might conclude that progress is slow.

Today, in contrast with one hundred and fifty years ago, the psychiatric patient who needs hospitalization is more generally recognized as a sick person rather than a criminal or dangerous one on whom humanitarian or considerate treatment would supposedly be wasted. And yet for the sensitive or sensible in modern, enlightened society, there remain shocking gaps.

In 35 of the states at the present time the mentally ill may legally be confined in jail while commitment is being effected. The actual occurrence of such incarceration is not statistically negligible. In half the states the mentally ill are legally named "insane" or "lunatic." Considering the might of the pen this kind of designation would not be in keeping with the best principles of mental hygiene, either for the patient or for the family.

The police, sheriffs or other officials of law enforcement are legally permitted, in 40 states, to implement the journey of the patient to a mental institution. Under existing laws, however practically helpful it may be to have recourse to the police, it is doubtfully helpful to the sick person or therapeutic for his illness to have to submit to the uniformed or unquestionable, symbolized presence of the law.

In many of the states numerous statutes regarding the hospitalization of the mentally ill are not consonant with the immediate and ultimate welfare of the patient. Along with the defects noted above are such legal deficiencies as mandatory trial by jury, in open court, with the patient present; no procedure for voluntary admission (commitment by court being required notwithstanding the willingness of the patient to ask for hospital care and treatment); after voluntary or emergency admission, a too swift legal commitment, in spite of the possibility of a comparatively early termination of the illness (commitment to a mental hospital is not usually regarded as an advantage in one's social or medical history); the right of the voluntary patient to release before his illness has been adequately studied; and indeterminate commitment without satisfactorily frequent review of status.

With the legally sane world behaving more and more oddly, it is gratifying that some of its noncommittable inhabitants are working for the benefit of their committable and committed brothers. Recently, the Federal Security Agency, in conjunction with the National Advisory Mental Health Council, drafted a "model law," which is called "An Act Governing Hospitalization of the Mentally Ill"* and which has been submitted to the governors of all the states. It is not expected that all state legislatures will or can revise existing legislation into nation-wide uniformity, but it is proposed that attention and action be directed toward "maximum opportunity for prompt medical care; protection against emotionally harmful or degrading treatment; protection against wrongful confinement and deprivation of rights."

In the problems accompanying hospital placement and care for the sick person, legal and medical considerations are of necessity intertwined. If the care is what it should be the law will be guided by medical opinion in determining what is best for the person in his inseparable relation with society. It is not claimed that the "model law" is flawless, but if state legislatures will at least attempt to make revisions sympathetic to its intent some of the suffering of the mentally ill may be alleviated, and respect for both law and psychiatry will be increased.

*A copy of the model law, with a commentary, may be obtained from the National Institute of Mental Health, Bethesda 14, Maryland.

SALE OF CHRISTMAS SEALS

From November 20 until Christmas the National Tuberculosis Association, as in previous years, appeals for contributions to the sale of Christmas Seals, whose proceeds constitute the entire support of the Association and its 3000 affiliated organizations in their campaign against tuberculosis through education, case finding, rehabilitation and medical research. Some facts about the disease and the progress made toward the goal of eradication bear repetition.

In spite of truly remarkable advances in prevention and treatment since the first sale of Christmas Seals in 1907, the problem of tuberculosis in terms of deaths, suffering, disability and economic loss remains formidable. Still one of the leading causes of death (the very first in the age group from fifteen to thirty-five years), the disease takes 40,000 lives a year in the United States, accounting for 1 out of every 30 deaths among whites and 1 out of every 13 among Negroes. A hundred thousand persons are attacked, and approximately 1,000,000 working years are sacrificed annually. Each year more than $350,000,000 is expended by public and private institutions for treatment, case finding, public-health nursing, health education and rehabilitation, among other activities, but this estimate does not include the costs of hospital construction or lost wages and lowered production.

Progress has been made in the effort to eradicate tuberculosis, but if these gains are to be held and extended, constant vigilance is necessary. The primary aim of all control programs is to discover unsuspected cases of disease in the early stages, the principal means to this end being mass x-ray examination. In 1949 approximately 14,000,000 small films of the chest were taken by health departments, tuberculosis associations and hospitals (so far as Boston is concerned, it has been stated that "the mass chest x-ray survey has been instrumental in detecting cases of tuberculosis earlier and has thus led to a lessening mortality and a greater number of reported cases"*). Streptomycin, in combination with para-aminosalicylic acid, is of great value in the therapy of certain types of the disease, and BCG (bacillus Calmette-Guérin) appears to offer protection, although the extent of the immunity afforded is still unknown. The new agents, combined with bed rest and operative intervention when necessary, offer hope to patients who would formerly have died of the disease.

The national and local associations are doing their utmost to advance control of tuberculosis toward the eventual goal of complete eradication. For their program to continue, generous donations are essential. Doctors should need no second urging to give their support to the sale of Christmas Seals, since they will thus be materially contributing to a campaign against a malady that kills more Americans each year than all other infectious diseases combined.

*Cauley, J. H. Results of Boston chest x-ray survey. *New Eng. J. Med.* 243:631-636, 1950.

In the October number of the New Hampshire Journal of Medicine, is an article by Dr. Garland, on a proposed "Remedy for Quackery." It is decidedly our opinion, that if the measure were adopted which is recommended by the writer of the article in question, the profession might be most emphatically placed in the same category with the class of whom they complain.

Boston M. & S. J., *November 20, 1850*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

Grover — Joseph I. Grover, M.D., of Wollaston, died on October 19. He was in his sixty-sixth year.

Dr. Grover received his degree from Harvard Medical School in 1911. He was a fellow of the American Medical Association.

His widow, two daughters and a son survive.

Hunter — Norman M. Hunter, M.D., of Hudson, died on November 5. He was in his seventy-eighth year.

Dr. Hunter received his degree from McGill University Faculty of Medicine in 1901. He was formerly medical examiner in the Hudson-Marlboro Area and was a fellow of the American College of Surgeons.

His widow, two sons, four grandchildren and two sisters survive.

Levins — Nathan N. Levins, M.D., of Boston, died on November 4. He was in his seventy-sixth year.

Dr. Levins received his degree from Tufts College Medical School in 1904. He was an associate fellow of the American Medical Association.

A daughter, a son and two brothers survive.

LYNCH — Charles F. Lynch, M.D., of Springfield, died recently. He was in his eightieth year.

Dr. Lynch received his degree from New York University Medical College in 1897. He was affiliated with the staffs of Springfield Health Department and Springfield hospitals and with the Wing Memorial Hospital in Palmer and was a fellow of the American College of Surgeons and American Medical Association. He was a fifty-year member of the Massachusetts Medical Society.

His widow and a sister survive.

REINISCH — Max Reinisch, M.D., of Holyoke, died on September 4. He was in his forty-fourth year.

Dr. Reinisch received his degree from Deutsche Universität Medizinische Fakultät, Prague, Czechoslovakia, in 1932. He was a member of the staffs of Holyoke and Providence hospitals and a fellow of the American Medical Association.

His widow survives.

BOSTON MEDICAL LIBRARY

SPANISH BOOKS

Spanish books of the sixteenth century in good condition are uncommon and command high prices. Because of climatic factors and neglect, the majority of such books are apt to be mildewed, incomplete and in bad condition. Dr. Bullard, when he traveled in Spain, procured a number of good to fine copies of important medical books, to which have been added a number purchased from a Mexican dealer.

The Library now has first editions of all the known existing books of the Spanish physician, Lobera d'Avila. The *Libro de las quatro enfermedades cortesanas* (Toledo, 1544) is recorded by Vindel, but a copy was not found by Palau. There is an Italian translation (Venice, 1558 and 1568). The 1558 edition is in the Library.

During 1950, two important additions were made to the Lobera d'Avila collection: *Vanquete de nobles cavalleros* (Augsburg, 1530), the first book of the author, and the German edition of the same book, under the title *Ein nutzlich Regiment der Gesundtheit, Genant das Vanquete* (Augsburg, 1531).

The Library has a fine set of the first medical periodical published in the Americas: the *Mercurio volante, con noticias importantes i curiosas sobre varios asuntos de fisica i medicina*, by doctor Josef Ignacio Bartolache, Mexico City. Sixteen numbers were published, October 17, 1772, to February 10, 1773. One other set exists in the United States, in the library of the American Philosophical Society, Philadelphia.

The Spanish collection is now available for consultation.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The December schedule for Consultation Clinics for Crippled Children in Massachusetts under the provisions of the Social Security Act follows:

Orthopedic Clinics	Date	Clinic Consultant
Lowell	December 1	Albert H. Brewster
Salem	December 4	Paul W. Hugenberger
Haverhill	December 6	William T. Green
Greenfield	December 7	Charles L. Sturdevant
Gardner	December 12	Carter R. Rowe
Brockton	December 14	George W. Van Gorder
Worcester	December 15	John W. O'Meara
Fall River	December 18	David S. Grice
Springfield	December 19	Garry deN. Hough, Jr.
Hyannis	December 28	Paul L. Norton

Rheumatic Fever Clinics	Dates
North Reading	December 5, 12, 19, 26
Fitchburg	December 6, 13, 20, 27

Plastic Clinics	Consultant
Eastern Massachusetts	Bradford Cannon
	Semi-monthly
Western Massachusetts	Joseph M. Baker
	Monthly

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

CORRESPONDENCE

EAST IS EAST AND WEST IS WEST

To the Editor: Your most recent editorial lamentations concerning the westerly migration of Boston-bred and Boston-trained physicians prompt me to chide you upon your geographical astigmatism and myopia since no one else seems to have done so. Dr. Ham's removal from Boston to Cleveland puts him about equidistant between the Mississippi and Boston, and it will take some fabulous gerrymandering or legislative benevolence to permit him to claim a home beyond the Mississippi. Perhaps the editors are bemused by the geographical notions of the *New Yorker* rather than the more objective versions of the Rand-McNally cartographers. The ways of an editor are hard, indeed.

I am sure that your numerous subscribers in the midlands are aware and thankful that your geographical obliquities betoken no similar disregard for medical facts in your excellent journal.

WILLIAM B. BEAN, M.D.

Iowa City, Iowa

BOOK REVIEWS

The Surgical Treatment of Facial Injuries. By Varaztad H. Kazanjian, M.D., D.M.D., and John M. Converse, M.D. 4°, cloth, 574 pp., with 746 illustrations. Baltimore: Williams and Wilkins Company, 1949. $10.00.

An extensive experience, both civil and military, has been combed to produce a text dealing with the treatment of acute facial injuries and the late deformities pertaining thereto. An introductory section presents the comparative anatomy of the major facial structures, followed by some general considerations of wound healing and basic principles of the technic of plastic surgery.

The section on the early treatment of facial injuries is devoted mainly to facial fractures and presents in well organized form methods that the senior author has developed or applied over many years of intensive study in this exacting field. The remainder of the book deals with plastic and reconstructive procedures used in the late treatment of facial deformities, including a discussion of free and pedicle grafting and a topographic consideration of lesions of the face, including the oral cavity and pharynx. In conclusion the uses of maxillofacial prostheses are briefly discussed.

One of the most valuable features is the wealth of graphic and informative sketches, well captioned and interspersed with relevant photographic material. This work will prove of interest not only to the plastic surgeon but also to the general surgeon and to the dental surgeon concerned with the care of fractures of the jaws.

Huang TiNei Ching Su Wên: The yellow emperor's classic of internal medicine. Chapters 1-34 translated from the Chinese with an introductory study. By Ilza Veith, M.A., Ph.D. 4°, cloth, 253 pp., with 24 illustrations and frontispiece. Baltimore: Williams and Wilkins Company, 1949. $5.00.

The *Nei Ching* of Huang Ti, the yellow emperor, is an important, if not the most important of the earliest Chinese medical classics. The book constitutes the basis of Chinese and Japanese orthodox medicine, and in China it is regarded as the most influential medical work in existence. It is tremendous in size, amounting to about 120,000 words in English translation. Miss Veith presents a translation of chapters one to thirty-four of the book. Preceding the translation is a very valuable essay on the Nei Ching and Chinese medicine, fully illustrated. This is a very valuable source book and should be in all collections of medical history.

Body and Mature Behavior: A study of anxiety, sex, gravitation and learning. By M. Feldenkrais. 8°, cloth, 167 pp. New York: International Universities Press, Incorporated, 1949. $3.75.

The author of this book advances the thesis that study and re-education of muscular behavior patterns, along with the analysis of the mental processes, are more effective in the understanding and treatment of emotional problems. Discussion is limited to the study of the factors that determine physiologic responses to emotional problems and a consideration of the development of human muscular behavior. The author also makes a plea for the study and the treatment of the organism as a whole, with emphasis on the re-education of the faulty muscular pattern, as well as on the re-education of the psychic reaction pattern.

The author considers that human carriage is the most dynamic of all the mammals and is primarily designed for action. He states that "erect carriage is assured by ease of dynamic adjustment to the position of maximum potential energy." Discussion of the relation between mobility and adjustment, normal gravitational adjustment and tonic adjustment are presented. Here, the author further illustrates how incorrect posture is a factor in emotional conditions. Incorrect posture as a result of reaction to emotional stress is a valuable consideration in the management of psychiatric problems. The author recognizes that posture re-education and reorientation are a part of the problem of therapy, and not a method of therapy in themselves. The chapter entitled "Muscular Habits and the Sexual Act" is the most valuable and informative of the entire book. Ideas developed here, although not new, are well discussed, and some practical information is given the reader.

The concept of muscular pattern and neurosis and the discussion of their development are well presented once they have been sifted from the other material present in this book. Unfortunately, the author has chosen a subject that has necessitated bridging the gaps among the various related disciplines in the study of human behavioral patterns. By way of background a review of neurophysiologic concepts necessary to understand and appreciate the point of view has been presented, and in this discussion there is much detail, and some of the concepts have been altered by more recent research.

NOTICES

ANNOUNCEMENTS

Dr. Anthony Alba announces the opening of an office at 199 Bay State Road, Boston, for the practice of ophthalmology.

Dr. Harry Freeman announces the removal of his office for the practice of medicine to 44 West Street, Worcester.

Dr. Milton E. Helman announces the opening of an office for the practice of dermatology at 1077A Blue Hill Avenue, Dorchester.

TUFTS MEDICAL ALUMNI LECTURE

The Annual Tufts Medical Alumni Lecture will be given at Tufts College Medical School on Tuesday, December 5, at 8 p.m. This lecture is given annually by a distinguished alumnus of Tufts College Medical School who is not on its faculty. Dr. Frederick W. Maroney, dean of students, Brooklyn College, New York, will speak on the subject "Protect the Power House."

Physicians, medical students and the faculty of Tufts College Medical School are invited to attend.

HARVARD MEDICAL SOCIETY

A meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, December 12, at 8 p.m. The program, presented by the Department of Physiology, Harvard Medical School, Dr. Landis, presiding, will be as follows:

The Cardiovascular Responses to Exercise of Dogs with Surgically Produced Cardiac Damage. A. C. Barger, J. Metcalfe, V. Richards, B. Gunther and W. Kinter.

Studies on the Physiology of Hibernation. P. O. Chatfield and C. P. Lyman.

The Interstitial Pressure in Mammalian Kidneys. C. W. Gottschalk.

Molecular Diffusion from Peripheral Capillaries, with Deductions Concerning the Number and Dimensions of Ultramicroscopic Openings in the Capillary Walls. J. R. Pappenheimer, E. M. Renkin and L. M. Borrere.

MASSACHUSETTS PHYSICIANS ART ASSOCIATION

The next meeting of the Massachusetts Physicians Art Association will be held in the Library of the Boston Lying-in Hospital on Wednesday, December 6, at 8 p.m. Mr. Ronald Murray will speak on his activities as art director of Houghton Mifflin Publishing Company.

Physicians are invited to attend.

NEW ENGLAND CARDIOVASCULAR SOCIETY

A special meeting of the New England Cardiovascular Society will be held at the Boston Medical Library, 8 the Fenway, Boston, on Monday, December 4, at 8 p.m. Dr. Ronald Grant, of Guy's Hospital, London, England, will be the guest speaker. The subject of his lecture will be announced later.

Interested physicians and medical students are cordially invited to attend.

NEW ENGLAND CONFERENCES ON ALLERGY AND RELATED SUBJECTS

The third New England Conference on Allergy and Related Subjects will take place on Wednesday afternoon and evening, December 13. The afternoon program will consist of the presentation of cases illustrating the use of Cortisone and ACTH, with special emphasis on recent advances. This part of the program will be held from 3 to 5 o'clock in the Stearns Amphitheater of the New England Center Hospital, 171 Harrison Avenue, Boston.

The evening program will take place in the Sheraton Room of the Copley Plaza Hotel, Boston, at 8:30 o'clock. A symposium will be held on the practical and theoretical aspects of the use of ACTH and Cortisone in allergic conditions.

Arrangements have been made for a dinner at the Copley Plaza Hotel, Boston, for the convenience of those attending

the program. Dinner will take place at 7:00 p.m., for which reservations may be made on or before December 11 by application to Dr. Irving W. Schiller, 65 East Newton Street, Boston 18, Massachusetts, enclosing a check for $4.75 to cover the expense of the dinner.

All members of the medical profession are cordially invited to both the afternoon and the evening meetings.

SPRINGFIELD HOSPITAL

The educational program of the Springfield Hospital for the month of December is as follows:

Saturday, December 2.

9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Radiology Conference on the subject "Diagnostic X-ray Problems of Special Interest" in the Staff Conference Room. Dr. John W. Turner.
11–12 noon. Combined Medical-Surgical Grand Rounds in the Staff Conference Room.

Saturday, December 9.

9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Seminar on Surgical Technic, Second Session in the Staff Conference Room. Dr. F. W. Hoyt and staff.
11–12 noon. Clinicopathological Conference in the Staff Conference Room.

Wednesday, December 13.

12–1 p.m. Psychosomatic-Medicine Conference on the subject "Anatomic Factors in Neurologic Disturbances" in the Staff Conference Room. Dr. Calvert Stein.

Thursday, December 14.

12:15 p.m. Staff Meeting in the Staff Room.

Saturday, December 16.

9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Pathology Conference: Seminar on Hematology in the Staff Conference Room. Dr. William Kaufmann.
11–12 noon. Medical-Death Review in the Staff Conference Room.

Tuesday, December 19.

8:30 p.m. Guest Speaker Conference on the subject "The Fear of Salt" in the Staff Conference Room. Dr. John P. Peters, professor of medicine, Yale University School of Medicine.

Wednesday, December 20.

12–1 p.m. Pathology Conference: Seminar on Hematology (continued) in the Staff Conference Room. Dr. William Kaufmann.

Saturday, December 23.

9–10 a.m. Grand Surgical Rounds.
10–11 a.m. Seminar on Surgical Technic, Third Session, in the Staff Conference Room. Dr. F. W. Hoyt and staff.
11–12 noon. Surgical-Death Review in the Staff Conference Room.

No conferences will be held between December 24, 1950, and January 2, 1951. All conferences, seminars and grand rounds, are open to interested physicians.

RHODE ISLAND MEDICAL SOCIETY

The midwinter meeting of the Rhode Island Medical Society will be held at the Blackstone Hotel, Woonsocket, Rhode Island, on Wednesday, December 13.

Program

4 p.m. Radiation Syndrome. Ernest K. Landsteiner, M.D., of Providence, and Joseph W. Howland, M.D., of Rochester, chief of the division of medical services of the Rochester Atomic Energy Project.

Pathology of Ionizing Radiation. Lieutenant Commander Russell Maynard, MC, USN, pathologist, the Newport Naval Hospital.

6:30 p.m. Dinner Session. Physician-Hospital Relations. Elmer Hess, M.D., of Erie, Pennsylvania (advance reservations required for dinner).

Additional information may be obtained from the Rhode Island Medical Society, 106 Francis Street, Providence 3.

SOCIETY MEETINGS AND CONFERENCES

November 1–29. Springfield Hospital. Page 679, issue of October 26.

November 27–June 4. New England Cardiovascular Society. Page 680, issue of October 26.

November 27. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

November 27. New England Cardiovascular Society. Page 798, issue of November 16.

November 27. Beth Israel Hospital House Officers' Colloquia. Page 798, issue of November 16.

November 28. Norfolk District Medical Society. Page 629, issue of October 19.

November 30. 94th Infantry Division Lecture. Page 798, issue of November 16.

December 2–23. Springfield Hospital. Notice above.

December 4. Beth Israel Hospital House Officers' Colloquia. Page 798, issue of November 16.

December 4. Hartford Medical Society. Page 680, issue of October 26.

December 4. New England Cardiovascular Society. Page 841.

December 5. Tufts Medical Alumni Lecture. Page 841.

December 6. Massachusetts Physicians Art Association. Page 841.

December 7–9. New York State Society of Anesthesiologists. Page 582, issue of October 12.

December 9. American Federation for Clinical Research. Page 680, issue of October 26.

December 12. Harvard Medical Society. Page 841.

December 13. Rhode Island Medical Society. Notice above.

December 13. New England Conferences on Allergy and Related Subjects. Page 841.

December 14. Treatment of Hyperthyroidism, Especially with Radioactive Iodine. Dr. Earle Chapman. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

December 18. Hartford Medical Society. Page 680, issue of October 26.

January 3. Hampshire District Medical Society. Page 170, issue of July 27.

January 22. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

January 23. Norfolk District Medical Society. Page 629, issue of October 19.

January 31. American Academy of Orthopaedic Surgery (see Kappa Delta Award for Research in Orthopedic Surgery). Page 736, issue of May 4.

February 13. New England Society of Anesthesiologists. Page 512, issue of September 28.

February 27. Norfolk District Medical Society. Page 629, issue of October 19.

March 26. Boston Lying-in Hospital Obstetric Round-Table Conference. Page 629, issue of October 19.

March 27. Norfolk District Medical Society. Page 629, issue of October 19.

April 9–13. American College of Physicians. Page 296, issue of June 15.

April 10. New England Society of Anesthesiologists. Page 512, issue of September 28.

April 24. Norfolk District Medical Society. Page 629, issue of October 19.

May 8. New England Society of Anesthesiologists. Page 512, issue of September 28.

May 9. Norfolk District Medical Society. Page 629, issue of October 19.

May 22–24. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

May 24–26. American Goiter Association. Columbus, Ohio.

November 10–21, 1951. Pan-Pacific Surgical Association. Page 680, issue of October 26.

District Medical Societies

HAMPSHIRE

January 3. 4:30 p.m. Veterans Administration Hospital, Northampton.
March 7. 4:30 p.m. Cooley-Dickinson Hospital, Northampton.
May 2. 4:30 p.m. Annual Meeting. Jones Library, Amherst.

NORFOLK

November 28.
January 23.
February 27.
March 27.
April 24.
May 9. Annual Dinner.

All meetings except the Annual Dinner will be held at the Boston Medical Library, 8 Fenway, at 8:00 p.m.

(Notices concluded on page xv)

NOTICES (*Concluded from page 842*)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 30

THURSDAY, NOVEMBER 30

*9:00–11:00 a.m. Medical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

FRIDAY, DECEMBER 1

*9:00–10:00 a.m. Medical Conference. Joseph H. Pratt Diagnostic Hospital.

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street, Boston.

*1:30 p.m. Tumor Clinic. Out-Patient Department, Mount Auburn Hospital, Cambridge.

SATURDAY, DECEMBER 2

*9:00–10:00 a.m. Surgical Grand Rounds. Joseph H. Pratt Diagnostic Hospital.

MONDAY, DECEMBER 4

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

*8:00 p.m. New England Cardiovascular Society. Boston Medical Library.

TUESDAY, DECEMBER 5

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*8:00 p.m. Tufts Medical Alumni Lecture. Tufts College Medical School.

WEDNESDAY, DECEMBER 6

*9:00–10:00 a.m. Medical Clinicopathological Conference. Joseph H. Pratt Diagnostic Hospital.

*12:00 m. X-Ray Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

*12:00 m.–1:00 p.m. Clinicopathological Conference. (Children's Medical Center.) Amphitheater, Peter Bent Brigham Hospital.

*8:00 p.m. Massachusetts Physicians Art Association. Boston Lying-in Hospital.

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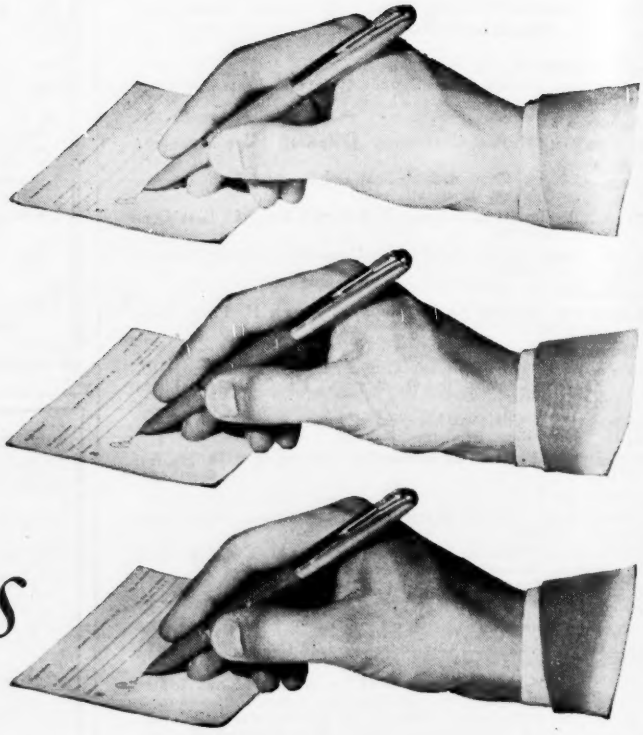

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